WO 2004/046323

PCT/US2003/036548

10/535042

STRUCTURE OF THE FARNESOID X RECEPTOR LIGAND BINDING DOMAIN AND METHODS OF USE THEREFOR

FIELD OF THE INVENTION

[0001] The present invention relates to the three-dimensional structure of farnesoid X receptors (FXR). In a particular aspect, the invention relates to compositions comprising the ligand binding domain of a FXR in crystalline form, as described by structure coordinates obtained by X-ray crystallography, and computers utilizing such structure coordinates to provide information regarding the ligand binding domain of FXRs and ligands therefor. In another aspect, the invention relates to methods of utilizing such structure coordinates for modeling of known and putative FXR ligands.

BACKGROUND OF THE INVENTION

[0002] Structural biology provides an important tool for the detailed characterization of proteins at the molecular level. This molecular approach can lead to a more complete understanding not only of a protein itself, for example, but also helps characterize the interactions between a ligand-binding protein and its known ligands and/or putative binding partners. The nuclear hormone receptor farnesoid X receptor (FXR) functions as a bile acid sensor by responding to physiological levels of a variety of bile acid ligands and coordinating the control and maintenance of lipid homeostasis. Elucidation of the three-dimensional structure, and in particular, the structure of the ligand binding domain involved in binding bile acids, can assist in studies of the function and physical properties of FXR.

[0003] An essential function of the liver and the intestine in vertebrates is to maintain lipid homeostasis within the body through tight regulation of the acquisition, synthesis and metabolism of cholesterol (Chawla et al. (2000). "Don't know much bile-ology". Cell. 103, 1-4). Excess cholesterol is either converted into bile acids in the liver, or undergoes biliary excretion in the intestine and is disposed of in the stool (Chiang (2002) Bile Acid regulation of gene expression: roles of nuclear hormone receptors. Endocr Rev. 23(4), 443-63). The

nuclear hormone receptor (NHR) farnesoid X receptor (FXR, also known as NRIH4) is involved in the regulation of both of these metabolic processes. FXR is expressed in the liver and intestine as well as other cholesterol rich tissues such as the adrenal gland. Knockout mice deficient in FXR expression display defects in bile acid (BA) homeostasis when exposed to dietary stresses, including elevated serum BA, reduced bile acid pools, and reduced fecal BA secretion (Sinal et al. (2000). Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. Cell: 102(6), 731-44). In the liver, the rate-limiting step for the conversion of excess cholesterol into bile acids is catalyzed by the cytochrome p450 gene, cholesterol 7alpha-hydroxylase (CYP7A1). A second cytochrome p450 gene, sterol 12 alpha-hydroxylase (CYP8B) is a key enzyme for regulating the cholic acid (CA)/chenodeoxycholic acid (CDCA) ratio in bile acid biosynthesis (Kerr et al., (2002) Loss of nuclear receptor SHP impairs but does not eliminate negative feedback regulation of bile acid synthesis. Dev Cell. 2(6), 713-20; Wang et al. (2002) Redundant pathways for negative feedback regulation of bile acid production. Dev Cell. 2(6), 721-31). In mammals these genes are indirectly regulated by FXR via the NHR homologue gene SHP (small heterodimer partner) (Lu et al. (2000). Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. Mol Cell. 6(3), 507-15; Goodwin et al (2000). A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell. 6(3), 517-26).

[0004] Physiological concentrations of specific BAs bind and activate FXR, the most potent being CDCA a major primary bile acid found in human bile (Makishima et al, (1999) Identification of a nuclear receptor for bile acids. Science. 284(5418), 1362-5; Parks et al. (1999). Bile acids: natural ligands for an orphan nuclear receptor. Science. 284(5418). 1365-8, and Wang et al. (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell. 3(5), 543-53). This activation enables FXR to act as a transcriptional sensor for bile acids (BAs), repressing the transcriptional expression of both CYP7A and CYP8B genes by increasing the levels of the inhibitory nuclear receptor SHP. SHP is a promiscuous inhibitory heterodimer partner of NHRs that suppresses the transcriptional activity of a large number of NHRs. However, its ability to bind and inhibit the liver receptor homologue (LRH-1) a NHR required for CYP7A gene expression, indirectly allows FXR to exert its influence on cholesterol homeostasis (Lu et al., (2000), supra; Goodwin et al., (2000), supra). Additionally, BA activation of FXR positively regulates the expression of genes

involved in the excretion and transportation of BAs including intestinal bile acid-binding protein (IBABP), bile salt export pump (BSEP) and canalicular multi-specific organic anion transporter (cMOAT) (Chiang (2002), supra). Thus, this receptor plays a key physiological role in the regulation of lipid homeostasis.

[0005] FXR belongs to a superfamily of ligand-inducible transcription factors involved in a wide array of biological functions including development, differentiation and homeostasis. The family members share two structurally-conserved domains; a central, highly conserved DNA binding domain (DBD) that targets the receptor to specific DNA sequences, termed hormone response elements, and a ligand binding domain (LBD) that binds small lipophilic hormones (Evans RM. (1988) The steroid and thyroid hormone receptor superfamily. Science. 240(4854), 889-95). The LBD functions as the regulating molecular switch. Binding of the appropriate hormone to the LBD causes a conformational change that results in the release of bound co-repressor proteins and the recruitment of co-activator proteins that culminates in the activation of transcriptional target genes. This regulation of NHR transcription factors by small lipophilic hormones makes this gene family an ideal target for chemical biology to identify novel chemical activators (Blumberg and Evans (1998). Orphan nuclear receptors--new ligands and new possibilities. Genes Dev. 12(20), 3149-55). FXR senses BA levels and mediates the repression of genes that convert excess cholesterol into bile BAs as well as the induction of BA transport genes makes FXR an attractive pharmaceutical target. The availability of potent synthetic agonists for FXR, and an understanding of how various binding agents interact with the ligand binding domain of FXR is a critical step required for the validation of FXR as a drug target and the elaboration of the functions of FXR.

SUMMARY OF THE INVENTION

[0006] The present invention provides the first high-resolution crystal structure determinations of a farnesoid X receptor (FXR) in its active state. Specifically disclosed herein is the ligand binding domain of FXR bound with a novel FXR agonist termed fexaramine, which is structurally distinct from known natural bile acid (BA) ligands. Accordingly, the invention provides a structural basis for understanding FXR ligand binding, and provides further knowledge of the physical properties of this receptor. The

present invention uses molecular modeling at the atomic level, to elucidate FXR-ligand interactions.

[0007] According to one aspect of the present invention, there are provided compositions comprising the ligand binding domain (LBD) of a FXR, and complexes thereof with ligands, in crystalline form. The invention further provides the structure coordinates of FXR complexed with fexaramine as determined by X-ray crystallography.

[0008] According to another aspect of the present invention, there is provided a computer for producing a three-dimensional representation of a FXR molecule or molecular complex or a homologue thereof, based on such FXR structure coordinates, or a portion thereof sufficient to define the points of interaction between a FXR LBD and a ligand therefor.

[0009] According to yet another aspect of the present invention, there is provided a computer for determining at least a portion of the structure coordinates corresponding to X-ray diffraction data obtained from a FXR molecule or molecular complex or a homologue thereof.

[0010] According to still another aspect of the present invention, there are provided methods of using the high-resolution crystal structure determinations of a farnesoid X receptor (FXR) in its active state. Specifically disclosed herein are methods of using the structure of the ligand binding domain (LBD) of FXR bound with a novel FXR agonist. Accordingly, the invention provides a structural basis for understanding FXR ligand binding, and provides further knowledge of the physical properties of this receptor. The present invention uses molecular modeling at the atomic level, to elucidate FXR-ligand interactions. By determining high-resolution x-ray crystal structures of a FXR complexed with a synthetic ligand, the present invention provides a more complete understanding of FXR structure and provides a molecular explanation of how both natural and modified or synthetic BAs interact with the receptor.

[0011] According to a further aspect of the present invention, there are provided methods of predicting a molecule capable of binding to a FXR molecule. Such methods comprise modeling a test molecule that potentially interacts with the LBD of FXR, wherein

the LBD is defined by a plurality of structure coordinates of the LBD of FXR. The structure coordinates of FXR are derived from X-ray diffraction data obtained from crystals of a FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex. In preferred embodiments, the structure coordinates correspond to the LBD of FXR complexed with the high affinity ligand fexaramine as described herein.

[0012] According to further aspects of the present invention, there are provided methods of identifying a compound with agonist, antagonist, or partial agonist activity for a FXR molecule. Such methods comprise modeling test compound using FXR structure coordinates. Also provided are compositions of compounds identified by such methods.

[0013] According to yet another aspect of the present invention, there are provided methods of determining whether a test compound is capable of binding to the LBD of a FXR molecule by analyzing and comparing points of interaction between the LBD and one or more FXR ligand(s), with points of interaction between the LBD and the test compound. In preferred embodiments, the test compound is a bile acid.

BRIEF DESCRIPTION OF THE FIGURES

[0014] **Figures 1A - 1C** collectively depict the activation of FXR by a variety of putative ligands.

[0015] **Figure 1A** depicts the selected regions of interest of prototypical structure lead compounds **1** used for further FXR ligand binding analysis. **Region I** denotes the right-hand aromatic system; **Region II** denotes the acyl group region; and **Region III** denotes the left-hand benzopyran ring system. Compound **2** was produced by systematic optimization of regions **I** and **II**. The novel compound termed fexaramine was discovered from a final 94-membered combinatorial library of region **III**.

[0016] **Figure 1B** illustrates the structures of lead compounds (and their EC_{50} values in a cell-based assay) selected for further biological evaluation as FXR agonists. Compound **A** is fexaramine (EC_{50}=25nM), compound **B** is fexarine (EC_{50}=38nM), compound **C** is fexarene (EC_{50}=36nM), compound **D** is SRI-1 (EC_{50}=377nM), and compound **E** is SRI-2 (EC_{50}=343nM). The identified compounds (**A-E**) are structurally distinct from known FXR agonists.

Compound F is CDCA, a biological low affinity endogenous agonist; and compound G is GW4064 (EC_{50}=80 nM), a high affinity agonist.

[0017] **Figure 1C** shows that the identified compounds fexaramine, fexarine, fexarene, SRI-1 and SRI-2 are agonist ligands for FXR *in vitro*. A FRET ligand-binding assay was carried out in agonist mode with GW4064 used as the control ligand. Increasing amounts of the compounds were added as indicated. Binding reactions contained 8 nM Europium labeled GST-FXR ligand-binding domain fusion protein and 16 nM allophycocyanin-labeled SRC-1 receptor binding peptide. Results are expressed at 1000*(665 nm/615 nm).

[0018] **Figures 2A – 2F** collectively show the results of ligand activation of CV-1 cells co-transfected with FXR constructs pCMX-mFXR and pCMX-hRXR and a luciferase reporter gene containing various promoters as follows: Figure 2A with a minimal TK promoter, Figure 2B with a TK-ECRE*6 promoter, Figure 2C with a TK-ER8*2 promoter, Figure 2D with hIBABP promoter, Figure 2E with a hPLTP promoter, or Figure 2 with a FhMRP-2 promoter. Increasing amounts (1 nM to 1 μM) of the compounds fexaramine, fexarine, fexarene, SRI-1, SRI-2 and GW4064 were added to the cells 24 hours post-transfection. Activation of the luciferase reporter gene was measured in relative light units (with β-galactosidase activity as a control for transfection efficiency) and presented as normalized luciferase units. Ligand response data were derived from triplicate points from two independent experiments and represented as the mean ± SE (n = 6).

[0019] **Figures 3A – 3E** collectively show the results of ligand activation of CV-1 cells co-transfected with a luciferase reporter gene with a variety of receptor expression constructs. Figure 3A shows the results of cells containing the MH2004 promoter-reporter construct that contains four GAL4 binding sites with pCMXGAL4-FXR LBD chimeric expression construct, treated with increasing amounts of the compounds fexaramine, fexarine, fexarene, SRI-1, SRI-2 and GW4064. Figure 3B shows the results of MH2004 promoter-reporter construct with pCMXGAL4-FXR LBD/RXRα constructs, treated with increasing amounts of the compounds fexaramine, fexarine, fexarene, SRI-1, SRI-2 and GW4064. Figures 3C – 3E show the results of CV-1 cells transiently transfected with the indicated reporter constructs, treated with either DMSO or 10 μM of the compounds fexaramine (3C), fexarine (3D), fexarene (3E). Reporter activity was normalized to the internal control and the data plotted

as fold activation relative to untreated cells. All transfections contained CMX-βgal as an internal control.

[0020] **Figures 4A – 4E** collectively show levels of various RNAs expressed in cells containing FXR receptors, in some cases treated with FXR ligands.

[0021] **Figure 4A** shows the respective RNAs expressed in HT29 stable cells cultured until confluence. 20 µg total RNA isolated using Trizol (Invitrogen) was used for Northern blot analysis. cDNA probes for mouse FXR and human IBABP were prepared and hybridized to the blot. Blots were normalized by β-actin expression.

[0022] **Figures 4B and 4C** show IBABP RNA expressed in HT29 stable cells that were cultured until confluence and then treated overnight with increasing amounts of CDCA (4B), GW4064 (4C) as indicated. 20 µg total RNA was isolated using Trizol (Invitrogen) and used for Northern blot analysis. cDNA probe for human IBABP was prepared and hybridized to the blot. Blots were normalized by β-actin expression.

[0023] **Figure 4D** shows IBABP RNA expressed in HT29-FXRFL stable cells that were cultured until confluence and then treated overnight with increasing amounts of the FXR ligands fexaramine, fexarine or fexarene as indicated. 20 µg total RNA was isolated using Trizol (Invitrogen) and used for Northern blot analysis. cDNA probe for human IBABP was prepared and hybridized to the blot. Blots were normalized by β-actin expression.

[0024] **Figure 4E** shows various FXR target molecule RNAs expressed inHEPG2-FXRFL stable cells that were cultured until confluence and then treated overnight with increasing amounts of FXR ligands fexaramine, fexarine, fexarene SRI-1, SRI-2, GW4064 (10 nM, 100 nM, 1 µM, 10 µM) and CDCA (10 µM, 25 µM, 50 µM, 100 µM). 20 µg total RNA was isolated using Trizol (Invitrogen) and used for Northern blot analysis. cDNA probes for human PLTP, SHP, MRP-2 and BSEP were prepared and hybridized to the blot. Blots were normalized by 36B4 expression as shown.

[0025] **Figure 5A** shows SHP RNA expression in ligand-treated primary mouse hepatocytes obtained from Cedera scientific and cultured in the appropriate medium. Twenty-four hours after delivery, hepatocytes were treated for 6 or 12 hours with either vehicle alone or 100 µM CDCA, 10 µM fexaraime, or 10 µM GW4064, as indicated. 10 µg

total RNA was isolated using Trizol (Invitrogen) and used for Northern blot analysis. The probe for human SHP was prepared and hybridized to the blot. To ensure constant loading of total RNA to the blot, GAPDH was also hybridized as a control.

[0026] **Figure 5B** is a clustergram of genes changed by FXR agonist treatment. Genes were identified using a paired Student's T-test and DMSO treatment as the control group. 222 transcripts were identified meeting a criteria of a change of at least 0.005 and a fold change with respect to DMSO of 2. Data was imported into Cluster and the genes were subjected to hierarchal clustering. The output was visualized using Treeview to monitor changes.

[0027] **Figure 5C** is a table of genes changed by FXR agonist treatment.

[0028] **Figures 6A – 6E** collectively illustrate the three-dimensional structure of the ligand-binding domain of human farnesoid X receptor (FXR).

[0029] **Figure 6A** is a three-dimensional representation of residues 248 to 270 and 286 to 476 of hFXR that were crystallized and examined in complex with the high affinity agonist, fexaramine. The α-helices are shown as ribbons and the ligand is shown within the ligand binding region within a transparent van der Waals surface. The structural elements are numbered according to the canonical structure for the LBD of nuclear receptors.

[0030] **Figure 6B** is a sequence alignment of the ligand binding domains of four human nuclear receptors, FXR, VDR, SXR, and RXRα. The secondary structural elements of the hFXR-LBD are shown above the FXR sequence.

[0031] **Figure 6C** is a close-up of the first set of points of interaction between the FXR LBD and fexaramine. The hexyl group protrudes out into solution while making weak van der Waals contact with two side chains; I339 and L344. The fexaramine carbonyl oxygen makes two hydrogen bonds, one with H298 and another with S336. The methyl ester aliphatic chain makes van der Waals contacts with Met294, Leu352 and I356. No charged interactions are seen in contact with the methyl ester moiety itself.

[0032] **Figure 6D** is a close-up of the second set of points of interactions set of points of interaction between the FXR LBD and fexaramine. The double benzyl rings make van der

Waals contact with 15 residues. The majority of the ligand binding pocket is hydrophobic in nature with the exception of Y365 and H451, which provide bulk and shape to the pocket through their ring systems.

[0033] **Figure 6E** is a close-up of a proposed model for binding of the natural ligand CDCA by FXR. CDCA was modeled upon the orientation of fexaramine with its hydroxyl groups pointed towards Y365 and H451 to accommodate hydrogen bonding. This positions the CDCA carboxyl group into the same orientation as the fexaramine hexyl group, suggesting that it protrudes from the protein or makes contacts with the insertion domain region. Glycine and taurine bile acid conjugates could be accommodated by this orientation.

[0034] **Figure 7** shows an example of a computer system in block diagram form.

DETAILED DESCRIPTION OF THE INVENTION

[0035] In accordance with the present invention, there are provided compositions comprising the ligand binding domain (LBD) of a farnesoid X receptor (FXR) in crystalline form. In accordance with a preferred embodiment of the present invention, there are provided high-resolution structures of FXR LBD complexed with a high affinity ligand, fexaramine, as described herein. The structure of a FXR LBD presented herein provides the first three-dimensional view of the structural basis for ligand binding between FXR and natural, modified and synthetic ligands therefor.

[0036] In accordance with the present invention, the crystal structure of the LBD of FXR complexed with fexaramine has been refined to 1.78 Å resolution. FXR LBD/fexaramine crystals belong to space group $P2_12_12_1$ with one molecule per asymmetric unit (52.9% solvent). Unit cell dimensions are about a = 36.656 Å, b = 56.776 Å, c = 117.646 Å , $\alpha=\beta=\gamma = 90.0$ °. The complete structure coordinates for the X-ray diffraction data set are set forth in Appendix 1.

[0037] One aspect of the invention resides in obtaining the FXR LBD in crystalline form, of sufficient quality to determine the three-dimensional structure of the protein by X-ray diffraction methods. X-ray crystallography is a method of solving the three-dimensional structures of molecules. The structure of a molecule is calculated from X-ray diffraction

patterns using a crystal as a diffraction grating. Three-dimensional structures of protein molecules arise from crystals grown from a concentrated solution of that protein. The process of X-ray crystallography can include the following steps:

(a) synthesizing and isolating a FXR LBD polypeptide;

(b) growing a crystal from a solution comprising the polypeptide with or without a ligand, or ligand analog; and

(c) collecting X-ray diffraction patterns from the crystals, determining unit cell dimensions and symmetry, determining electron density, fitting the amino acid sequence of the polypeptide to the electron density, and refining the structure.

[0038] The term "crystalline form" refers to a crystal formed from a solution comprising a purified polypeptide corresponding to all or part of FXR. In preferred embodiments, a crystalline form may also be formed from a purified polypeptide corresponding to all or part of FXR in a complex with one or more additional known or putative ligand molecules, or other known or putative molecules capable of binding to FXR or an FXR homologue, such as natural, synthetic, or modified bile acids.

[0039] In accordance with another embodiment of the present invention, there are provided methods utilizing structure coordinates obtained by X-ray crystallography of crystals comprising the ligand binding domain (LBD) of a farnesoid X receptor (FXR). In accordance with a preferred aspect of this embodiment of the present invention, the methods utilize information obtained from high-resolution structures of FXR LBD complexed with a high affinity ligand fexaramine as described herein. The structure of a FXR LBD presented herein provides the first three-dimensional view of the structural basis for ligand binding between FXR and natural, modified and synthetic ligands therefor.

[0040] According to one aspect of the present invention, there are provided methods of predicting a molecule capable of binding to a farnesoid X receptor (FXR) molecule, said method comprising: modeling a test molecule that potentially interacts with the ligand binding domain of said FXR molecule, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, and wherein said structure coordinates are derived from X-ray diffraction data obtained from

crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex.

[0041] FXR was first reported by Forman *et al.*, (1995). Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 81:687-693. This receptor is a protein having a relative molecular mass of approximately 54,000 Daltons, and is a vertebrate transcription factor regulated by intracellular metabolites. The receptor is activated by certain farnesoids, *i.e.*, farnesol itself and compounds derived from, and/or similar in structure to, farnesol. These farnesoids include farnesol, farnesal, farnesyl acetate, farnesoic acid, geranylgeraniol, and juvenile hormone III.

[0042] FXR polypeptides contemplated for use in the practice of the present invention can be characterized by reference to the unique tissue distribution thereof. Thus, expression of FXR polypeptides is restricted to the liver, gut, adrenal gland and kidney, all tissues known to have a significant flux through the mevalonate pathway. U.S. Patent No. 6,184,353 to Evans *et al.*, which is hereby incorporated by reference herein in its entirety, describes the characteristics of a murine FXR protein.

[0043] Presently preferred human FXR polypeptides contemplated for use in the practice of the present invention can be characterized as having substantially the same amino acid sequence as SEQ ID NO:1, a representative human FXR (see below). Especially preferred FXR polypeptides contemplated for use in the practice of the present invention are those which have the same amino acid sequence as SEQ ID NO:1, or a fragment thereof. The LBD of SEQ ID NO:1 corresponds to approximately C-terminal amino acid residues 248-476. An alternative human FXR polypeptide for use in the methods of the present invention is provided as SEQ ID NO:2 (see below). The LBD of SEQ ID NO:2 corresponds to approximately C-terminal amino acid residues 244-472, and is identical to the LBD of SEQ ID NO:1.

SEQ ID NO:1 Human FXR amino acid sequence (Q96RI1)

```
1   MGSKMNLIEH SHLPTTDEFS FSENLFGVLT EQVAGPLGQN LEVEPYSQYS
NVQFPQVQPQ
61  ISSSSYYSNL GFYPQQPEEW YSPGIYELRR MPAETLYQGE TEVAEMPVTK
KPRMGASAGR
121 IKGDELCVVC GDRASGYHYN ALTCEGCKGF FRRSITKNAV YKCKNGGNCV
MDMYMRRKCQ
```

181 ECRLRKCKEM GMLAECMYTG LLTEIQCKSK RLRKNVKQHA DQTVNEDSEG
RDLRQVTSTT
241 KSCREKTELT PDQQTLLHFI MDSYNKQRMP QEITNKILKE EFSAEENFLI
LTEMATNHVQ
301 VLVEFTKKLP GFQTLDHEDQ IALLKGSAVE AMFLRSAEIF NKKLPSGHSD
LLEERIRNSG
361 ISDEYITPMF SFYKSIGELK MTQEEYALLT AIVILSPDRQ YIKDREAVEK
LQEPLLDVLQ
421 KLCKIHQPEN PQHFACLLGR LTELRTFNHH HAEMLMSWRV NDHKFTPLLC EIWDVQ

SEQ ID NO:2 Human FXR amino acid sequence (AAB08017)

1 MGSKMNLIEH SHLPTTDEFS FSENLFGVLT EQVAGPLGQN LEVEPYSQYS
NVQFPQVQPQ
61 ISSSSYYSNL GFYPQQPEEW YSPGIYELRR MPAETLYQGE TEVAEMPVTK
KPRMGASAGR
121 IKGDELCVVC GDRASGYHYN ALTCEGCKGF FRRSITKNAV YKCKNGGNCV
MDMYMRRKCQ
181 ECRLRKCKEM GMLAECLLTE IQCKSKRLRK NVKQHADQTV NEDSEGRDLR
QVTSTTKSCR
241 EKTELTPDQQ TLLHFIMDSY NKQRMPQEIT NKILKEEFSA EENFLILTEM
ATNHVQVLVE
301 FTKKLPGFQT LDHEDQIALL KGSAVEAMFL RSAEIFNKKL PSGHSDLLEE
RIRNSGISDE
361 YITPMFSFYK SIGELKMTQE EYALLTAIVI LSPDRQYIKD REAVEKLQEP
LLDVLQKLCK
421 IHQPENPQHF ACLLGRLTEL RTFNHHHAEM LMSWRVNDHK FTPLLCEIWD VQ

[0044] The phrase "substantially the same" is used herein in reference to amino acid sequences that have slight and non-consequential sequence variations from the actual sequences disclosed herein. Species which are "substantially the same" as the reference sequence are considered to be equivalent to the disclosed sequences and as such are within the scope of the appended claims. The amino acid sequences of FXRs of a variety of species are readily available to one of skill in the art using public databases, such as through the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), accessible on the World Wide Web (www) at the URL "ncbi.nlm.nih.gov".

[0045] An FXR homologue as used herein, refers to a FXR molecule that has the same ligand binding properties as the FXR molecule identified in SEQ ID NO:1.

[0046] Alternatively, a farnesoid activated receptor polypeptides contemplated for use in the practice of the present invention can be characterized by:

(1) being responsive to the presence of farnesoid(s) to regulate the transcription of associated gene(s);

(2) having a relative molecular mass of about 54,000 Daltons; and

(3) having a DNA binding domain of about 66 amino acids with 9 Cys residues, wherein said DNA binding domain has:

(a) about 81% amino acid identity with the DNA binding domain of the Drosophila ecdysone receptor,

(b) about 56% amino acid identity with the DNA binding domain of VDR, and

(c) about 45% amino acid identity with the DNA binding domain of hGR.

[0047] FXR polypeptides contemplated for use in the practice of the present invention can be further characterized by: having a ligand binding domain of about 220 amino acids, wherein said ligand binding domain has:

(a) about 33% amino acid identity, and about 59% amino acid similarity, with the ligand binding domain of the Drosophila ecdysone receptor,

(b) about 32% amino acid identity with the ligand binding domain of VDR, and

(c) about 26% amino acid identity with the ligand binding domain of hGR.

[0048] FXR polypeptides contemplated for use in the present invention include those derived from vertebrates, mammals, murine species, humans, and the like.

[0049] The amino acid sequence of a contemplated FXR contains several features that are consistent as being a member of the nuclear receptor superfamily. The region spanning about amino acid residues 124 - 289 contains several invariant amino acids, including 4 cysteine residues that are characteristic of the DNA binding domain (DBD) of all nuclear hormone receptors. The DBD of a murine FXR is most similar to the DBD of the insect ecdysone receptor (EcR). These receptors share about 81% amino acid sequence identity within their DBDs.

[0050] In addition, the carboxy-terminal LBD of nuclear receptors is a complex region encoding subdomains for ligand binding, dimerization and transcriptional activation. Analysis of the carboxy terminal region of a murine FXR indicates that it possesses only about 33% sequence identity (59% similarity) with the corresponding region of the ecdysone receptor. Within this region, significant similarity is confined to regions involved in receptor

dimerization (see, *e.g.*, Forman and Samuels (1990) *Mol. Endocrinol.* 4:1293-1301), including the Ti subdomain (48% identity), heptad repeats 4-6 (50% identity) and heptad 9 (75% identity). In addition, the last 22 amino acids, which possess transcriptional activation functions in other receptors (see Danielian *et al.*, *EMBO J.* 11:1025-1033 (1992)), are 42% identical among FXR and EcR. These structural similarities indicate that FXR is a member of the nuclear receptor superfamily.

[0051] As used herein, the phrase "amino acid sequence similarity" refers to sequences which have amino acid substitutions which do not change the inherent chemical properties of the subject polypeptide. Thus, amino acid sequences wherein an acidic residue is replaced with another acidic residue, or wherein a basic residue is replaced with another basic residue, or wherein a neutral residue is replaced with another neutral residue, retain a high degree of similarity with respect to the original sequence, notwithstanding the fact that the sequences are no longer identical.

[0052] The term "ligand" as used herein refers to a molecule that is capable of binding to a FXR polypeptide or portion thereof. The term "agonist" as used herein refers to a molecule that binds to and activates a receptor polypeptide or portion thereof. The term "antagonist" as used herein refers to a molecule that attenuates the effect of an agonist. The term "partial agonist" as used herein refers to an agonist that is incapable of producing maximal activation of a receptor, as compared to a full agonist, at any concentration.

[0053] Ligands that are suitable for use in the methods and compositions of the invention include, but are not limited to, bile acids (natural, modified or synthetic) and related compounds such as CDCA (chenodeoxycholic acid), GCDCA (glycochenodeoxycholic acid), TCDCA (taurochenodeoxycholic acid), GCA (glycocholic acid), TCA (taurocholic acid), DCA (deoxycholic acid), LCA (lithocholic acid), DHCA (dehydrocholic acid), UDCA (ursodeoxycholic acid) and CA (cholic acid).

[0054] Bile acids are derivatives of cholesterol synthesized in the hepatocyte. Cholesterol, ingested as part of the diet or derived from hepatic synthesis is converted into the bile acids cholic and chenodeoxycholic acids, which are then conjugated to an amino acid (glycine or taurine) to yield the conjugated form that is actively secreted into cannaliculi. Bile acids are facial amphipathic, that is, they contain both hydrophobic (lipid

soluble) and polar (hydrophilic) faces. The cholesterol-derived portion of a bile acid has one face that is hydrophobic (that with methyl groups) and one that is hydrophilic (that with the hydroxyl groups); the amino acid conjugate is polar and hydrophilic.

[0055] Any compounds that are capable of binding to the LBD of FXR can also be used in methods and compositions of the present invention. In a presently preferred embodiment, the ligand is selected from the group consisting of fexaramine, fexarine, fexarene and GW4064, the structures of which are presented in Figure 1. An endogenous agonist, such as the bile acid CDCA can also be crystallized and/or modeled according the methods of the present invention. Additional bile acids and other ligands are described in, for example, Makishima *et al.* (1999), supra. Methods and compositions described herein can also employ coactivators and corepressors with which FXR interacts.

[0056] Any test compound can be tested for its ability to regulate or modulate transcription-activating effects of a farnesoid activated receptor polypeptide using the following exemplary method. Host cells containing a FXR LBD, or transfected with a FXR LBD expression construct, may be transfected with a target reporter construct encoding a reporter protein, such as luciferase. When cells containing both a FXR LBD and a reporter construct as below are contacted with a test compound that has agonist activity, expression of the reporter protein is activated, and the reporter is detected. When cells containing both a FXR LBD and a reporter construct as below are contacted with a known agonist in addition to a test compound that has antagonist activity, the level of expression of the reporter protein is decreased relative to the level of expression in the presence of the known agonist alone. When cells containing both a FXR LBD and a reporter construct as below are contacted with a test compound that has partial agonist activity, the level of expression of the reporter protein is decreased relative to the level of expression in the presence of a known agonist, even at the highest concentrations of the compound that is a partial agonist.

[0057] The reporter construct in this exemplary system comprises: (a) a promoter that is operable in said cell, (b) a hormone response element that is responsive to the DNA binding domain of the receptor (FXR DBD if native or alternative DBD if FXR is chimeric), and (c) DNA encoding a reporter protein, wherein said reporter protein-encoding DNA segment is

operatively linked to said promoter for transcription of said DNA segment, and wherein said promoter is operatively linked to said hormone response element for activation thereof.

[0058] Other molecules are also capable of binding to a FXR polypeptide or portion thereof. Such molecules include any compound that can interact with the ligand binding domain of a FXR themselves, or prevent access of another molecule to the ligand binding domain of a FXR by binding to FXR at another location, for example, small chemical compounds (natural, modified or synthetic), drugs, other polypeptides or proteins, antibodies, nucleic acids, or the like.

[0059] Test molecules or test compounds may be developed de novo, or from a known ligand of FXR, such as a bile acid (natural, modified or synthetic). Test molecules may also be developed using a computer algorithm to predict a three-dimensional representation of the test molecule interacting with a FXR based upon a three-dimensional representation of A FXR molecule or fragment thereof.

[0060] According to another aspect of the present invention, there are provided methods of identifying a compound with agonist activity for a farnesoid X receptor (FXR) molecule, said method comprising:

(a) modeling a test compound that potentially interacts with the ligand binding domain of said FXR molecule or a fragment thereof, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof,

wherein said plurality of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex; and

(b) determining the ability of said test compound to activate said FXR molecule.

[0061] According to another aspect of the present invention, there are provided methods of identifying a compound with antagonist activity for a farnesoid X receptor (FXR) molecule, said method comprising:

(a) modeling a test compound that potentially interacts with the ligand binding domain of said FXR molecule or a fragment thereof, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof,

wherein said plurality of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex; and

(b) determining the ability of said test compound to modulate the activity of said FXR molecule in the presence of a known FXR agonist.

[0062] According to another aspect of the present invention, there are provided methods of identifying a compound with partial agonist activity for a farnesoid X receptor (FXR) molecule, said method comprising:

(a) modeling a test compound that potentially interacts with the ligand binding domain of said FXR molecule or a fragment thereof, wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof,

wherein said plurality of structure coordinates are derived from X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex; and

(b) determining the ability of said test compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist.

[0063] Any agonist of FXR or potential agonist may be used in such methods. Typically, a test compound exhibiting antagonist activity tested in combination with a known agonist will decrease the level of activity or activation of FXR as compared to the level of activity or activation of FXR in the presence of the agonist alone. Typically, a test compound exhibiting partial agonist activity will not activate FXR to the same level as a known agonist, regardless of the concentrations tested.

[0064] In preferred embodiments, said plurality of structure coordinates are set forth in Appendix 1, or a portion thereof sufficient to define the points of interaction between said ligand binding domain and a ligand therefor.

[0065] Also provided are compositions of compounds identified by such methods, as well as pharmaceutical compositions comprising such compounds and a pharmaceutically acceptable carrier therefor.

[0066] According to the present invention, a FXR polypeptide comprising the LBD of FXR can be synthesized and isolated using methods that are well known in the art. Nucleic acid sequences encoding a FXR or a portion thereof can be produced by the methods described herein, or any alternative methods available to the skilled artisan. In designing the nucleic acid sequence of interest, it may be desirable to reengineer the gene for improved expression in a particular expression system. For example, it has been shown that many bacterially derived genes do not express well in plant systems. In some cases, plant-derived genes do not express well in bacteria. This phenomenon may be due to the non-optimal G+C content and/or A+T content of the gene relative to the expression system being used. For example, the very low G+C content of many bacterial genes results in the generation of sequences mimicking or duplicating plant gene control sequences that are highly A+T rich. The presence of A+T rich sequences within the genes introduced into plants (*e.g.*, TATA box regions normally found in promoters) may result in aberrant transcription of the gene(s). In addition, the presence of other regulatory sequences residing in the transcribed mRNA (*e.g.*, polyadenylation signal sequences (AAUAAA) or sequences complementary to small nuclear RNAs involved in pre-mRNA splicing) may lead to RNA instability. Therefore, one goal in the design of genes is to generate nucleic acid sequences that have a G+C content that affords mRNA stability and translation accuracy for a particular expression system.

[0067] Due to the plasticity afforded by the redundancy of the genetic code (*i.e.*, many amino acids are specified by more than one codon), evolution of the genomes of different organisms or classes of organisms has resulted in differential usage of redundant codons. This "codon bias" is reflected in the mean base composition of protein coding regions. For example, organisms with relatively low G+C contents utilize codons having A or T in the third position of redundant codons, whereas those having higher G+C contents utilize

codons having G or C in the third position. Therefore, in reengineering genes for expression, one may wish to determine the codon bias of the organism in which the gene is to be expressed. The usage of codons for genes of a particular organism can be determined by analyzing such genes that have been deposited in GenBank or other databases containing nucleotide sequence information. After determining the bias thereof, the new gene sequence can be analyzed for restriction enzyme sites as well as other sites that could affect transcription such as exon:intron junctions, polyA addition signals, or RNA polymerase termination signals.

[0068] Genes encoding a FXR polypeptide comprising the LBD of FXR can be placed in an appropriate vector, depending on the artisan's interest, and can be expressed using a suitable expression system. An expression vector, as is well known in the art, typically includes elements that permit replication of said vector within the host cell and may contain one or more phenotypic markers for selection of cells containing said gene. The expression vector will typically contain sequences that control expression such as promoter sequences, ribosome-binding sites, and translational initiation and termination sequences. Expression vectors may also contain elements such as subgenomic promoters, a repressor gene or various activator genes. The artisan may also choose to include nucleic acid sequences that result in secretion of the gene product, movement of said product to a particular organelle such as a plant plastid (see, *e.g.*, U.S. Patent Nos. 4,762,785; 5,451,513 and 5,545,817, which are incorporated by reference herein) or other sequences that increase the ease of peptide purification, such as an affinity tag.

[0069] A wide variety of expression control sequences are useful in expressing the gene encoding the polypeptide when operably linked thereto. Such expression control sequences include, for example, the early and late promoters of SV40 for animal cells, the lac system, the trp system, major operator and promoter systems of phage S, and the control regions of coat proteins, particularly those from RNA viruses in plants. In *E. coli*, a useful transcriptional control sequence is the T7 RNA polymerase binding promoter, which can be incorporated into a pET vector as described by Studier *et al.*, Meth. Enzymol. 185:60-89 (1990), which is incorporated by reference herein.

[0070] For expression, a desired gene should be operably linked to the expression control sequence and maintain the appropriate reading frame to permit production of the desired polypeptide. Any of a wide variety of well-known expression vectors are of use in the practice of the present invention. These include, for example, vectors comprising segments of chromosomal, non-chromosomal and synthetic DNA sequences such as those derived from SV40, bacterial plasmids including those from *E. coli* such as col E1, pCR1, pBR322 and derivatives thereof, pMB9, wider host range plasmids such as RP4, phage DNA such as phage S, NM989, M13, and other such systems as described by Sambrook *et al.*, (MOLECULAR CLONING, A LABORATORY MANUAL, 2nd Ed. (1989) Cold Spring Harbor Laboratory Press), which is incorporated by reference herein.

[0071] A wide variety of host cells are available for expressing polypeptides of the present invention. Such host cells include, for example, bacteria such as *E. coli*, *Bacillus* and *Streptomyces*, fungi, yeast, animal cells, plant cells, insect cells, and the like. Preferred embodiments of the present invention include FXR polypeptides comprising the LBD of FXR that are expressed in *E. coli* with a histidine tag to facilitate purification.

[0072] Once a polypeptide of the present invention is expressed, the protein obtained therefrom can be isolated or purified so that structural analysis, modeling, and/or biochemical analysis can be performed, as exemplified herein. The nature of the protein obtained can be dependent on the expression system used. For example, genes, when expressed in mammalian or other eukaryotic cells, may contain latent signal sequences that may result in glycosylation, phosphorylation, or other post-translational modifications, which may or may not alter function. Therefore, a preferred embodiment of the present invention is the expression of FXR genes or portions thereof in *E. coli* cells. Once such proteins are expressed, they can be easily purified using techniques common to the person having ordinary skill in the art of protein biochemistry, such as, for example, techniques described in Colligan *et al.* (CURRENT PROTOCOLS IN PROTEIN SCIENCE, Chanda, Ed., John Wiley & Sons, Inc., (1997)), which is incorporated by reference herein. Such techniques often include the use of cation-exchange or anion-exchange chromatography, gel filtration-size exclusion chromatography, and the like. Another technique that may be commonly used is affinity chromatography. Affinity chromatography can include the use of antibodies, substrate analogs, or histidine residues (His-tag technology as preferred herein).

[0073] By a "substantially pure polypeptide" is meant a polypeptide which has been separated from components which naturally accompany it. Typically, the polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, polypeptide of interest. A substantially pure polypeptide may be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding the polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method (*e.g.*, column chromatography, polyacrylamide gel electrophoresis, by HPLC analysis, and the like).

[0074] Once purified, the present invention allows for the characterization of FXR polypeptides comprising the LBD of FXR by crystallization followed by X-ray diffraction. Polypeptide crystallization occurs in solutions where the polypeptide concentration exceeds it solubility maximum (*i.e.*, the polypeptide solution is supersaturated). Such solutions may be restored to equilibrium by reducing the polypeptide concentration, preferably through precipitation of the polypeptide crystals. Often polypeptides may be induced to crystallize from supersaturated solutions by adding agents that alter the polypeptide surface charges or perturb the interaction between the polypeptide and bulk media to promote associations that lead to crystallization.

[0075] Compounds known as "precipitants" are often used to decrease the solubility of the polypeptide in a concentrated solution by forming an energetically unfavorable precipitating layer around the polypeptide molecules (Weber, *Adv. Prot. Chem.* **41**:1-36 (1991)). In addition to precipitants, other materials are sometimes added to the polypeptide crystallization solution. These include buffers to adjust the pH of the solution and salts to reduce the solubility of the polypeptide. Various precipitants are known in the art and include, for example, ethanol, 3-ethyl-2-4 pentanediol, many of the polyglycols, such as polyethylene glycol, and the like.

[0076] Commonly used polypeptide crystallization methods include, for example, batch, hanging drop, seed initiation, and dialysis methods. In each of these methods, it is important to promote continued crystallization after nucleation by maintaining a

supersaturated solution. In the batch method, the polypeptide is mixed with precipitants to achieve supersaturation, the vessel is sealed, and set aside until crystals appear. In the dialysis method, the polypeptide is retained in a sealed dialysis membrane that is placed into a solution containing precipitant. Equilibration across the membrane increases the polypeptide and precipitant concentrations thereby causing the polypeptide to reach supersaturation levels.

[0077] In the preferred hanging drop technique (McPherson, *J. Biol. Chem.* 251:6300-6303 (1976)), an initial polypeptide mixture is created by adding a precipitant to a concentrated polypeptide solution. The concentrations of the polypeptide and precipitants are such that in this initial form, the polypeptide does not crystallize. A small drop of this mixture is placed on a glass slide that is inverted and suspended over a reservoir of a second solution. The system is then sealed. Typically, the second solution contains a higher concentration of precipitant or other dehydrating agent. The difference in the precipitant concentrations causes the protein solution to have a higher vapor pressure than the second solution. Since the system containing the two solutions is sealed, an equilibrium is established, and water from the polypeptide mixture transfers to the second solution. This equilibrium increases the polypeptide and precipitant concentration in the polypeptide solution. At the critical concentration of polypeptide and precipitant, a crystal of the polypeptide will form.

[0078] Another method of crystallization involves introducing a nucleation site into a concentrated polypeptide solution. Generally, a concentrated polypeptide solution is prepared and a seed crystal of the polypeptide is introduced into this solution. If the concentrations of the polypeptide and of any precipitants are correct, the seed crystal will provide a nucleation site around which a larger crystal forms.

[0079] Some proteins may be recalcitrant to crystallization. However, several techniques are available to the skilled artisan. Quite often the removal of polypeptide segments at the amino or carboxy terminal end of the protein is necessary to produce crystalline protein samples. Said procedures involve either the treatment of the protein with one of several proteases including trypsin, chymotrypsin, substilisin, and the like. This treatment often results in the removal of flexible polypeptide segments that are likely to negatively affect crystallization. Alternatively, the removal of coding sequences from the

protein's gene facilitates the recombinant expression of shortened proteins that can be screened for crystallization. In preferred embodiments of the present invention, only the LBD of FXR, amino acid residues 248 – 476 of SEQ ID NO:1, is expressed for crystallization.

[0080] The crystals so produced have a wide range of uses. For example, high quality crystals are suitable for X-ray or neutron diffraction analysis to determine the three-dimensional structure of a FXR, to design mutants thereof, to determine ligand binding properties and pharmacokinetics thereof, and the like. In addition, crystallization can serve as a further purification method. In some instances, a polypeptide or protein will crystallize from a heterogeneous mixture into crystals. Isolation of such crystals by methods known in the art, for example, filtration, centrifugation, and the like, followed by redissolving the polypeptide affords a purified solution suitable for use in growing the high-quality crystals needed for diffraction studies. The high-quality crystals may also be dissolved in water and then formulated to provide an aqueous solution having other uses as desired.

[0081] Because FXR polypeptides may crystallize in more than one crystal form, the structure coordinates of a FXR or portions thereof, as provided by this invention, are particularly useful to solve the structure of other crystal forms of a FXR polypeptide. Said structure coordinates, as provided herein in Appendix 1, may also be used to solve the structure of FXR homologues or portions therof.

[0082] The structure coordinates disclosed herein may be used to determine the structure of the crystalline form of other proteins with significant amino acid or structural homology to any functional domain of a FXR. One method that may be employed for such purpose is molecular replacement. In this method, the unknown crystal structure, whether it is another crystal form of a FXR, a FXR having a mutation of one or more amino acid position(s), or the crystal of some other protein with significant sequence and/or structural homology to a FXR, may be determined using the coordinates provided herein. This method provides structural information for the unknown crystal in sufficient detail for further evaluation, and is more efficient than attempting to determine such information *ab initio*. In addition, this method can be used to determine whether or not a given FXR molecule in question falls within the scope of this invention.

[0083] The terms " structure coordinates", "structural coordinates", " atomic coordinates", "data set", "X-ray coordinates" or "X-ray data coordinates" as used herein are interchangeable, and refer to a data set (or portions thereof) that defines the three-dimensional structure of a molecule, for example, as set forth in Appendix 1. In particular, the LBD of FXR can be defined by a particular set of points of interaction between specific amino acid residues of the FXR LBD and a ligand therefor, for example, as illustrated in Figures 6C - 6E. Amino acid residues of FXR that may be used as reference points of interaction to define the LBD include two or more of Phe288, Leu291, Thr292, Met294, Ala295, His298, Met332, Phe333, Ser336, Ile339, Phe340, Leu344, Leu352, Ile356, Ile361, Tyr365, Met369, Phe370, Tyr373, His451, Met454, Leu455, Trp458, Phe465, Leu469, and Trp473.

[0084] In preferred embodiments, crystals of the LBD of FXR complexed with the high affinity agonist fexaramine belong to space group $P2_12_12_1$, with unit cell dimensions of about a = 37 Å, b = 57 Å, c = 117 Å , and $\alpha=\beta=\gamma = 90$ °. The data sets are derived from mathematical equations related to the patterns obtained on diffraction of a monochromatic beam of X-rays by the atoms (scattering centers) of a protein molecule in crystal form. The diffraction data are used to calculate an electron density map of the repeating unit of the crystal cell. Structure coordinates can be slightly modified and still render nearly identical three-dimensional structures. A measure of a unique set of structure coordinates is the root-mean-square (r.m.s.) deviation of the resulting structure. Structure coordinates that render three-dimensional structures that deviate from one another by an r.m.s. deviation of less than about 1.5 Å may be viewed as identical since they have little effect on the overall structure, and would not significantly alter the nature of binding associations. Furthermore, those of skill in the art understand that a set of coordinates for a polypeptide or portion thereof, is a relative set of points that define the three-dimensional shape of said polypeptide or portion thereof. As such, it is possible that an entirely different set of structure coordinates could define a similar or identical shape. Hence, the structure coordinates set forth in Appendix 1 are not limited to the express values set forth therein.

[0085] X-ray crystallography can elucidate the three-dimensional structure of crystalline forms according to the invention. Typically, the first characterization of crystalline forms by X-ray crystallography can determine the unit cell shape and its orientation in the crystal.

The term "unit cell" refers to the smallest and simplest volume element of a crystal that is completely representative of the unit of pattern of the crystal. The dimensions of the unit cell are defined by six numbers: dimensions a, b and c and angles α, β and γ. A crystal can be viewed as an efficiently packed array of multiple unit cells. Detailed descriptions of crystallographic terms are provided in Hahn, THE INTERNATIONAL TABLES FOR CRYSTALLOGRAPHY, VOLUME A, 4th Ed., Kluwer Academic Publishers (1996); and Shmueli, THE INTERNATIONAL TABLES FOR CRYSTALLOGRAPHY, VOLUME B, 1st Ed., Kluwer Academic Publishers. The term "space group" refers to the symmetry of a unit cell. In a space group designation (*e.g.*, P2) the capital letter indicates the lattice type and the other symbols represent symmetry operations that can be carried out on the unit cell without changing its appearance.

[0086] The term "selenomethionine substitution" refers to the method of producing a chemically modified form of a protein crystal. The protein is expressed by bacteria in media that is depleted in methionine and supplement with selenomethionine. Selenium is thereby incorporated into the crystal in place of methionine sulfurs. The location(s) of selenium is(are) determined by X-ray diffraction analysis of the crystal. This information is used to generate the phase information used to construct a three-dimensional structure of the protein.

[0087] "Heavy atom derivatization" refers to a method of producing a chemically modified form of a protein crystal. In practice, a crystal is soaked in a solution containing heavy atom salts or organometallic compounds, *e.g.*, lead chloride, gold thiomalate, thimerosal, uranyl acetate, and the like, which can diffuse through the crystal and bind to the protein's surface. Locations of the bound heavy atoms can be determined by X-ray diffraction analysis of the soaked crystal. This information is then used to construct phase information which can then be used to construct three-dimensional structures of the enzyme as described in Blundel and Johnson, PROTEIN CRYSTALLOGRAPHY, Academic Press (1976), which is incorporated by reference herein.

[0088] The knowledge obtained from X-ray diffraction patterns can be used in the determination of the three-dimensional structure of the binding sites of other homologous polypeptides. This is achieved through the use of commercially available software known in

the art that is capable of generating three-dimensional graphical representations of molecules or portions thereof from a set of structure coordinates. The binding domain can also be predicted by various computer models. Based on the structural X-ray coordinates of the solved structure, mutations and variants of the solved structure can also be designed.

[0089] According to another aspect of the present invention, there is provided a computer method for producing a three-dimensional representation of a FXR molecule or molecular complex or a homologue of said molecule or molecular complex, wherein said molecule or molecular complex or a homologue of said molecule or molecular complex comprises a LBD defined by structure coordinates obtained from X-ray diffraction data obtained from crystals of said FXR molecule of molecular complex or a homologue thereof. Said computer comprises:

(i) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex;

(ii) a working memory for storing instructions for processing said computer-readable data;

(iii) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-machine readable data into said three-dimensional representation; and

(iv) a display coupled to said central-processing unit for displaying said three-dimensional representation.

[0090] In preferred embodiments, the structure coordinates are set forth in Appendix 1, or a portion thereof sufficient to define the points of interaction between said LBD and a ligand therefor. The points of interaction can be one or more amino acid residues of the LBD which come into contact with or proximity with a molecule capable of binding the FXR LBD, as illustrated in Figure 6.

[0091] The term "molecular complex" as used herein refers to a FXR polypeptide or portion thereof combined with one or more additional molecules. For example, in preferred embodiments, the contemplated molecular complex comprises the FXR LBD together with a

high affinity agonist, such as, for example, fexaramine, fexarene, ortho-fluoro-fexarene, and the like.

[0092] According to another aspect of the present invention, there is provided a computer for determining at least a portion of the structure coordinates corresponding to X-ray diffraction data obtained from a FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex, said computer comprising:

(i) a computer-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structure coordinates of Appendix 1;

(ii) a computer-readable data storage medium comprising a data storage material encoded with computer-readable data, wherein said data comprises X-ray diffraction data obtained from said FXR molecule or molecular complex or a homologue of said FXR molecule or molecular complex;

(iii) a working memory for storing instructions for processing said computer-readable data of (i) and (ii);

(iv) a central-processing unit coupled to said working memory and to said computer-readable data storage medium of (i) and (ii) for performing a Fourier transform of the machine readable data of (i) and for processing said computer-readable data of (ii) into structure coordinates; and

(v) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

[0093] The term "computer" as used herein can be composed of a central processing unit (for example, the Pentium III from Intel Corporation, or similar processor from Sun, Motorola, Compaq, AMD or International Business Machines, and the like), a working memory which may be random-access memory or core memory, mass storage memory (for example, one or more floppy disk drives, compact disk drives or magnetic tape containing data recorded thereon), at least one display terminal, at least one keyboard and accompanying input and output devices and connections therefor. The computer typically includes a mechanism for processing, accessing and manipulating input data. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable. It should also be noted that the computer can be linked to other computer systems

in a network or wide area network to provide centralized access to the information contained within the computer.

[0094] Contemplated input devices for entering machine readable data include, for example, telephone modem lines, cable modems, CD-ROMs, a keyboard or disk drives. The computer may advantageously include or be programmed with appropriate software for reading the data from the data storage component or input device, for example computational programs for use in rational drug design that are described in detail below. Contemplated output devices include conventional systems known in the art, for example, display terminals, printers, or disk drives for further storage of output.

[0095] Embodiments of the invention include systems (*e.g.*, internet based systems), particularly computer systems which store and manipulate the coordinate and sequence information described herein. One example of a computer system **100** is illustrated in block diagram form in Figure 7. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the coordinates and sequences such as those set forth in Appendix 1. The computer system **100** typically includes a processor for processing, accessing and manipulating the sequence data. The processor **105** can be any well-known type of central processing unit, such as, for example, the Pentium III from Intel Corporation, or similar processor from other suppliers such as Sun, Motorola, Compaq, AMD or International Business Machines.

[0096] Typically the computer system **100** is a general purpose system that comprises the processor **105** and one or more internal data storage components **110** for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

[0097] In one particular embodiment, the computer system **100** includes a processor **105** connected to a bus which is connected to a main memory **115** (preferably implemented as RAM) and one or more internal data storage devices **110**, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system **100** further includes one or more data retrieving device(s) **118** for reading the data stored on the internal data storage devices **110**.

[0098] The data retrieving device **118** may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, a modem capable of connection to a remote data storage system (*e.g.*, via the internet), and the like. In some embodiments, the internal data storage device **110** is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, and the like, containing control logic and/or data recorded thereon. The computer system **100** may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device.

[0099] The computer system **100** includes a display **120** which is used to display output to a computer user. It should also be noted that the computer system **100** can be linked to other computer systems **125a-c** in a network or wide area network to provide centralized access to the computer system **100**.

[0100] Software for accessing and processing the coordinate and sequences of Appendix 1, (such as search tools, compare tools, and modeling tools etc.) may reside in main memory **115** during execution.

[0101] Computer programs are widely available that are capable of carrying out the activities necessary to model structures and substrates using the crystal structure information provided herein. Examples include, but are not limited to, the computer programs listed below:

Catalyst Databases™ - an information retrieval program accessing chemical databases such as BioByte Master File, Derwent WDI and ACD;
Catalyst/HYPO™ - generates models of compounds and hypotheses to explain variations of activity with the structure of drug candidates;
Ludi™ - fits molecules into the active site of a protein by identifying and matching complementary polar and hydrophobic groups;
Leapfrog™ - "grows" new ligands using an algorithm with parameters under the control of the user.

[0102] In addition, various general purpose machines may be used with programs written in accordance with the teachings herein, or it may be more convenient to construct more specialized apparatus to perform the operations. However, preferably this is implemented in

one or more computer programs executing on programmable systems each comprising at least one processor, at least one data storage system (including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. The program is executed on the processor to perform the functions described herein.

[0103] "Molecular replacement" refers to generating a preliminary model of a polypeptide whose structure coordinates are unknown, by orienting and positioning a molecule whose structure coordinates are known within the unit cell of the unknown crystal so as to best account for the observed diffraction pattern of the unknown crystal. Phases can then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. This in turn can be subject to any of the several forms of refinement to provide a final, accurate structure of the unknown crystal (Lattman, *Meth. Enzymol.* 115:55-77 (1985); Rossmann, MG., ed., THE MOLECULAR REPLACEMENT METHOD (1972), Int. Sci. Rev. Ser. No. 13, Gordon & Breach, New York). Using structure coordinates of the FXR LBD provided herein, molecular replacement may be used to determine the structure coordinates of a crystalline mutant, homologue, or a different crystal form of a FXR LBD.

[0104] In accordance with this invention, a FXR polypeptide, or a portion thereof such as the LBD, may be crystallized in association or complex with any known or putative ligands. The crystal structures of a series of such complexes may then be solved by molecular replacement and compared with that of a native FXR molecule. Potential sites for modification within the FXR molecule or a corresponding ligand may thus be identified based on the points of interaction between a ligand and the LBD of FXR. This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between FXR and a putative chemical entity or compound, even before any synthesis or modifications are performed.

[0105] All of the complexes referred to above may be studied using well-known X-ray diffraction techniques as described herein, and may be refined versus 2-3 Å resolution X-ray data to an R value of about 0.20 or less using computer software, such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.). See, *e.g.*, Blundel & Johnson, *supra*; Methods in Enzymology, vol. 114 and 115, H. W. Wyckoff *et al.*, eds., Academic Press

(1985). This information may thus be used to optimize known classes of FXR binding agents or ligand, such as natural bile acids, and to design, modify and/or synthesize novel classes of FXR ligands.

[0106] The modeling or design of compounds or ligands that bind to and/or modulate a FXR polypeptide according to the invention generally involves consideration of two factors. First, the compound or molecule must be capable of physically and structurally associating with a FXR molecule. Non-covalent molecular interactions important in the association of a FXR with a putative ligand include hydrogen bonding, van der Waals and hydrophobic interactions, and the like.

[0107] Second, the compound or molecule must be able to assume a conformation that allows it to associate with a FXR molecule. Although certain portions of the compound or molecule will not directly participate in this association, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on affinity with the receptor. Such conformational requirements include the overall three-dimensional structure and orientation of the compound or molecule in relation to all or a portion of the binding site, *e.g.*, LBD or any potential accessory binding sites, or the spacing between functional groups of a compound or molecule comprising several chemical entities that directly interact with FXR.

[0108] The term "modeling" as used herein, refers to analysis of the interaction of FXR and a known or test compound or molecule by utilizing a computer generated representation of the molecules, as opposed to physical molecules.

[0109] The potential binding of a test compound with a FXR may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and FXR, synthesis and testing of the compound may be obviated. However, if computer modeling indicates a strong interaction, the molecule may then be tested for its ability to bind to FXR. Methods of assaying for FXR activity are known in the art (as identified and discussed herein). Methods for assaying the effect of a potential binding agent can be performed in the presence of a known binding agent of FXR. For example, the effect of the potential binding

agent can be assayed by measuring the ability of the potential binding agent to compete with a known binding agent.

[0110] A test compound may be computationally evaluated and designed by means of a series of steps in which chemical entities or fragments are screened and selected for their ability to associate with the individual binding pockets or other areas of FXR associated with ligand binding. In particular, the ability to form points of interaction with the approximately 25 amino acid residues of the LBD identified earlier and depicted in Figure 6 can be assessed.

[0111] One skilled in the art may use one of several methods to predict a molecule capable of binding to FXR and to screen test compounds for their ability to associate with a FXR and more particularly with the individual binding pockets or LBD of a FXR polypeptide. This process may begin by visual inspection of, for example, the LBD on the computer screen based on structure coordinates obtained derived from X-ray diffraction data obtained from crystals of FXR, such as those provided in Appendix 1. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within an individual binding pocket of the FXR LBD. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMM and AMBER.

[0112] Specialized computer programs may also assist in the process of selecting fragments or chemical entities at this stage. These include:

1. GRID (Goodford, P. J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.
2. MCSS (Miranker, A. and M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure. Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.
3. AUTODOCK (Goodsell, D. S. and A. J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure. Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla, Calif.

4. DOCK (Kuntz, I. D. *et al.*, "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

[0113] Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound that is a candidate ligand. Assembly may be performed by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of the FXR molecule as set forth in Appendix 1. This would be followed by manual model building using software such as Quanta or Sybyl.

[0114] Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (Bartlett, P. A. et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In "Molecular Recognition in Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.
2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif.). This area is reviewed in Martin, Y. C., "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992)).
3. HOOK (available from Molecular Simulations, Burlington, Mass.).

[0115] In addition to the method of building or identifying a ligand in a step-wise fashion one fragment or chemical entity at a time as described above, FXR ligands may be designed as a whole or "de novo" using either an empty LBD site or optionally including some portion(s) of a known ligand(s). These methods include:

1. LUDI (Bohm, H.-J., "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comp. Aid. Molec. Design, 6, pp. 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, Calif.
2. LEGEND (Nishibata, Y. and A. Itai, Tetrahedron, 47, p. 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, Mass.
3. LeapFrog (available from Tripos Associates, St. Louis, Mo.).

[0116] Other molecular modeling techniques may also be employed in accordance with this invention. See, *e.g.*, Cohen, N. C. *et al.*, "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990). See also, Navia, M. A. and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

[0117] Once a test compound or binding agent has been designed or selected by the above methods, the efficiency with which that compound may bind to a FXR may be tested and optimized by computational evaluation.

[0118] A compound designed or selected as a putative ligand may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target site. Such non-complementary (*e.g.*, electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the binding agent and FXR when the ligand is bound to the FXR, preferably make a neutral or favorable contribution to the enthalpy of binding.

[0119] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C (M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa., 1992); AMBER, version 4.0 (P. A. Kollman, University of California at San Francisco, 1994); QUANTA/CHARMM (Molecular Simulations, Inc., Burlington, Mass. 1994); and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif., 1994). These programs may be implemented, for example, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art of which the speed and capacity are continually modified.

[0120] Other molecular modeling techniques may also be employed in accordance with this invention. For exemplary reviews and techniques, see, *e.g.*, Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, J. Med. Chem., 33, pp. 883-894 (1990); see also, M. A. Navia and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992); L. M. Balbes et al., "A Perspective of Modern Methods in Computer-Aided Drug Design", in Reviews in

Computational Chemistry, Vol. 5, K. B. Lipkowitz and D. B. Boyd, Eds., VCH, New York, pp. 337-380 (1994); see also, W. C. Guida, "Software For Structure-Based Drug Design", Curr. Opin. Struct. Biology, 4, pp. 777-781 (1994)]

[0121] In another embodiment of the present invention, the crystal structure and structure coordinates may be employed for the design of novel therapeutics. The transactivating capability of FXR on multiple target genes can be modified in new ways with novel compounds identified herein.

[0122] Bile acid synthesis is a major pathway for cholesterol disposal and thus represents a potential therapeutic target pathway for the treatment of hypercholesterolemia. FXR acts as a bile acid receptor and biological sensor for the regulation of bile acid biosynthesis. FXR is known to regulate cholesterol metabolism in two ways: (1) chenodeoxycholic acid (CDCA), a primary bile acid, binds directly to and activates FXR, which then mediates the feedback suppression by bile acids of cholesterol 7 alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid biosynthesis from cholesterol; and (2) FXR participates in the activation of intestinal bile acid binding protein (IBABP), which is involved in the enterohepatic circulation of bile acids. Thus FXR constitutes a potential therapeutic target that can be modulated to enhance the removal of cholesterol from the body. Novel compounds identified by the methods presented herein provide a new tool for regulating or modulating FXR function.

[0123] Furthermore, FXR is known to in turn activate a series of target genes. In particular FXR functions as a heterodimer with the 9-cis-retinoic acid receptor (RXR). A number of target DNA binding sequences that would be present in target genes have recently been identified. A consensus sequence has been determined, which contains an inverted repeat of the sequence AGGTCA with a 1-base pair spacing (IR-1) (Laffitte *et al.* (2000) Identification of the DNA binding specificity and potential target genes for the farnesoid X-activated receptor. *J. Biol. Chem.* 275:10638-10647). This sequence was shown to be a high affinity binding site for FXR/RXR *in vitro* and to confer ligand-dependent transcriptional activation by FXR/RXR to a heterologous promoter in response to a bile acid or synthetic retinoid. Although these studies demonstrated that the FXR/RXR heterodimer binds to the consensus IR-1 sequence with the highest affinity, it was also demonstrated that

FXR/RXR can bind to and activate through a variety of elements including IR-1 elements with changes in the core half-site sequence, spacing nucleotide, and flanking nucleotides. In addition, it was shown that FXR/RXR can bind to and transactivate through direct repeats. Therefore, by providing novel ways to modulate FXR function, the present invention in turn provides a method of modulating the function of a variety of target genes that are acted upon by FXR.

[0124] A FXR modulating agent or compound identified by the methods of the present invention may be administered with a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer to a subject suffering from bile acid imbalances, for example. Any appropriate route of administration may be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, oral administration, or the like. Therapeutic formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets, capsules or the like; and for intranasal formulations, in the form of powders, nasal drops, aerosols, or the like.

[0125] Methods well known in the art for making formulations are found in, for example, Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412, 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for IAP modulatory agents include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, liposomes, and the like. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[0126] The following terms are provided to facilitate the reader's understanding of the crystal compositions of FXR provided herein.

[0127] "Isolated" refers to a protein or nucleic acid that has been identified and separated from its natural environment. Contaminant components of its natural environment may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In one embodiment, the isolated molecule, in the case of a protein, will be purified to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence or to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or silver stain. In the case of a nucleic acid the isolated molecule will preferably be purified to a degree sufficient to obtain a nucleic acid sequence using standard sequencing methods.

[0128] As used herein, "naturally occurring amino acid" and "naturally occurring R-group" includes L-isomers of the twenty amino acids naturally occurring in proteins. Naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine. Unless specially indicated, all amino acids referred to in this application are in the L-form.

[0129] "Unnatural amino acid" and "unnatural R-group" includes amino acids that are not naturally found in proteins. Examples of unnatural amino acids included herein are racemic mixtures of selenocysteine and selenomethionine. In addition, unnatural amino acids include the D or L forms of, for example, nor-leucine, para-nitrophenylalanine, homophenylalanine, para-fluorophenylalanine, 3-amino-2-benzylpropionic acid, homoarginines, D-phenylalanine, and the like.

[0130] "R-group" refers to the substituent attached to the α-carbon of an amino acid residue. An R-group is an important determinant of the overall chemical character of an amino acid. There are twenty natural R-groups found in proteins, which make up the twenty naturally occurring amino acids.

[0131] "α-carbon" refers to the chiral carbon atom found in an amino acid residue. Typically, four substituents will be covalently bound to said α-carbon including an amine

group, a carboxylic acid group, a hydrogen atom, and an R-group. The α-carbon atoms can also be referred to by their crystal structure coordinates as a convenient reference point.

[0132] "Positively charged amino acid" and "positively charged R-group" includes any naturally occurring or unnatural amino acid having a side chain, which is positively charged under normal physiological conditions. Examples of positively charged, naturally occurring amino acids include arginine, lysine, histidine, and the like.

[0133] "Negatively charged amino acid" and "negatively charged R-group" includes any naturally occurring or unnatural amino acid having a side chain, which is negatively charged under normal physiological conditions. Examples of negatively charged, naturally occurring amino acids include aspartic acid, glutamic acid, and the like.

[0134] "Hydrophobic amino acid" and "hydrophobic R-group" includes any naturally occurring or unnatural amino acid that is relatively insoluble in water. Examples of naturally occurring hydrophobic amino acids are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, methionine, and the like.

[0135] "Hydrophilic amino acid" and "hydrophilic R-group" includes any naturally occurring or unnatural amino acid that is relatively soluble in water. Examples of naturally occurring hydrophilic amino acids include serine, threonine, tyrosine, asparagine, glutamine, cysteine, and the like.

[0136] "Degenerate variations thereof" refers to changing a gene sequence using the degenerate nature of the genetic code to encode proteins having the same amino acid sequence yet having a different gene sequence. For example, FXRs of the present invention are based on amino acid sequences. Degenerate gene variations thereof can be made encoding the same protein due to the plasticity of the genetic code, as described herein.

[0137] "Expression" refers to transcription of a gene or nucleic acid sequence, stable accumulation of nucleic acid, and the translation of that nucleic acid to a polypeptide sequence. Expression of genes also involves transcription of the gene to make RNA, processing of RNA into mRNA in eukaryotic systems, and translation of mRNA into proteins. It is not necessary for the genes to integrate into the genome of a cell in order to achieve expression. This definition in no way limits expression to a particular system or to

being confined to cells or a particular cell type and is meant to include cellular, transient, *in vitro, in vivo,* and viral expression systems in both prokaryotic, eukaryotic cells, and the like.

[0138] "Foreign" or "heterologous" genes refers to a gene encoding a protein whose exact amino acid sequence is not normally found in the host cell.

[0139] "Promoter" and "promoter regulatory element", and the like, refers to a nucleotide sequence element within a nucleic acid fragment or gene that controls the expression of that gene. These can also include expression control sequences. Promoter regulatory elements, and the like, from a variety of sources can be used efficiently to promote gene expression. Promoter regulatory elements are meant to include constitutive, tissue-specific, developmental-specific, inducible, subgenomic promoters, and the like. Promoter regulatory elements may also include certain enhancer elements or silencing elements that improve or regulate transcriptional efficiency. Promoter regulatory elements are recognized by RNA polymerases, promote the binding thereof, and facilitate RNA transcription.

[0140] A polypeptide is a chain of amino acids, regardless of length or post-translational modification (*e.g.*, glycosylation or phosphorylation). A polypeptide or protein refers to a polymer in which the monomers are amino acid residues, which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-isomers being typical. An exemplary FXR polypeptide of the invention is provided as an amino acid sequence set forth in SEQ ID NO:1.

[0141] Accordingly, the polypeptides of the invention are intended to cover naturally occurring proteins, as well as those which are recombinantly or synthetically synthesized. Polypeptide or protein fragments are also encompassed by the invention. Fragments can have the same or substantially the same amino acid sequence as the naturally occurring protein. A polypeptide or peptide having substantially the same sequence means that an amino acid sequence is largely, but not entirely, the same, but retains a functional activity of the sequence to which it is related. In general polypeptides of the invention include peptides, or full-length protein, that contains substitutions, deletions, or insertions into the protein backbone, that would still have an approximately 70%-90% homology to the original protein over the corresponding portion. A yet greater degree of departure from homology is allowed if like-

amino acids, *i.e.* conservative amino acid substitutions, do not count as a change in the sequence.

[0142] A polypeptide may be substantially related but for a conservative variation, such polypeptides being encompassed by the invention. A conservative variation denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. Other illustrative examples of conservative substitutions include the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine, glutamine, or glutamate; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; valine to isoleucine or leucine, and the like. The term "conservative variation" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

[0143] Modifications and substitutions are not limited to replacement of amino acids. For a variety of purposes, such as increased stability, solubility, or configuration concerns, one skilled in the art will recognize the need to introduce, (by deletion, replacement, or addition) other modifications. Examples of such other modifications include incorporation of rare amino acids, dextra-amino acids, glycosylation sites, cytosine for specific disulfide bridge formation. The modified peptides can be chemically synthesized, or the isolated gene can be site-directed mutagenized, or a synthetic gene can be synthesized and expressed in bacteria, yeast, baculovirus, tissue culture, and so on.

[0144] The term "variant" refers to polypeptides modified at one or more amino acid residues yet still retain the biological activity of a FXR polypeptide. Variants can be produced by any number of means known in the art, including, for example, methods such as, for example, error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly

PCR, sexual PCR mutagenesis, and the like, as well as any combination thereof. Variants of FXR may also be FXR proteins, or isoforms or homologues naturally found in other species

[0145] By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 60%, more preferably 70%, more preferably 80%, more preferably 85%, more preferably 90%, and most preferably 95% homology to a reference amino acid or nucleic acid sequence.

[0146] Sequence homology and identity are often measured using sequence analysis software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). The term "identity" in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same when compared and aligned for maximum correspondence over a comparison window or designated region as measured using any number of sequence comparison algorithms or by manual alignment and visual inspection. The term "homology" in the context of two or more nucleic acids or polypeptide sequences, refers to two or more sequences or subsequences that are homologous or have a specified percentage of amino acid residues or nucleotides that are homologous when compared and aligned for maximum correspondence over a comparison window or designated region as measured using any number of sequence comparison algorithms or by manual alignment and visual inspection. Programs as mentioned above allow for amino acid substitutions with similar amino acids matches by assigning degrees of homology to determine a degree of homology between the sequences being compared.

[0147] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0148] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequence for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Person & Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection. Other algorithms for determining homology or identity include, for example, in addition to a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information), ALIGN, AMAS (Analysis of Multiply Aligned Sequences), AMPS (Protein Multiple Sequence Alignment), ASSET (Aligned Segment Statistical Evaluation Tool), BANDS, BESTSCOR, BIOSCAN (Biological Sequence Comparative Analysis Node), BLIMPS (BLocks IMProved Searcher), FASTA, Intervals & Points, BMB, CLUSTAL V, CLUSTAL W, CONSENSUS, LCONSENSUS, WCONSENSUS, Smith-Waterman algorithm, DARWIN, Las Vegas algorithm, FNAT (Forced Nucleotide Alignment Tool), Framealign, Framesearch, DYNAMIC, FILTER, FSAP (Fristensky Sequence Analysis Package), GAP (Global Alignment Program), GENAL, GIBBS, GenQuest, ISSC (Sensitive Sequence Comparison), LALIGN (Local Sequence Alignment), LCP (Local Content Program), MACAW (Multiple Alignment Construction & Analysis Workbench), MAP (Multiple Alignment Program), MBLKP, MBLKN, PIMA (Pattern-Induced Multi-sequence Alignment), SAGA (Sequence Alignment by Genetic Algorithm) and WHAT-IF. Such alignment programs can also be used to screen genome databases to identify polynucleotide sequences having substantially identical sequences. A number of genome databases are available, for example, a substantial portion of the human genome is available as part of the Human Genome Sequencing Project (J. Roach, accessible on the world wide web (www) at the URL "weber.u.Washington.edu/~roach/ human_ genome_ progress 2.html") (Gibbs, 1995). Several databases containing genomic information annotated with some functional information are maintained by different

organization, and are accessible via the internet on the world wide wed (www), for example, at the URL "tigr.org/tdb"; "genetics.wisc.edu"; "genome-www.stanford.edu/~ball"; "hiv-web.lanl.gov"; "ncbi.nlm.nih.gov"; "ebi.ac.uk"; "Pasteur.fr/other/biology"; and "genome.wi.mit.edu".

[0149] One example of a useful algorithm is BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al., Nucl. Acids Res.* 25:3389-3402 (1977), and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990), respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information on the world wide web (www) at the URL "ncbi.nlm.nih. gov". This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al., supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectations (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N= -4, and a comparison of both strands.

[0150] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin & Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873 (1993)). One measure of similarity provided by BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or

amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a references sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0151] In one embodiment, protein and nucleic acid sequence homologies are evaluated using the Basic Local Alignment Search Tool ("BLAST") In particular, five specific BLAST programs are used to perform the following task:

(1) BLASTP and BLAST3 compare an amino acid query sequence against a protein sequence database;

(2) BLASTN compares a nucleotide query sequence against a nucleotide sequence database;

(3) BLASTX compares the six-frame conceptual translation products of a query nucleotide sequence (both strands) against a protein sequence database;

(4) TBLASTN compares a query protein sequence against a nucleotide sequence database translated in all six reading frames (both strands); and

(5) TBLASTX compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

[0152] The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (*i.e.*, aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet *et al.*, Science 256:1443-1445 (1992); Henikoff and Henikoff, Proteins 17:49-61 (1993)). Less preferably, the PAM or PAM250 matrices may also be used (see, *e.g.*, Schwartz and Dayhoff, eds., *Matrices for Detecting Distance Relationships: Atlas of Protein Sequence and Structure*, Washington: National Biomedical Research Foundation (1978)). BLAST programs are accessible through the U.S. National Library of Medicine, *e.g.*, accessible on the world wide web (www) at ncbi.nlm.nih.gov.

[0153] The parameters used with the above algorithms may be adapted depending on the sequence length and degree of homology studied. In some embodiments, the parameters may be the default parameters used by the algorithms in the absence of instructions from the user.

[0154] A detailed description of FXR LBD structure is provided below as a preferred embodiment of the invention.

[0155] The crystal structure of the ligand binding domain (LBD) of human FXR (hFXR, amino acids 248-476 of SEQ ID NO:1) in complex with the novel potent agonist identified herein, fexaramine was determined to 1.78 Å resolution. The hFXR LBD adopts a 12 alpha helix bundle as seen in all NHR LBD structures (RXRα (Egea et al. (2000). Crystal structure of the human RXRa ligand-binding domain to its natural ligand: 9-cis retinoic acid EMBO J. 19, 2592-2601), PXR/SXR (Watkins et al. (2001). The Human Nuclear Xenobiotic Receptor PXR: Structural Determinants of Directed Promiscuity, Science, 292, 2329-2333), PPARγ (Xu et al. (2001). Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. Proc Natl Acad Sci U S A. 98(24), 13919-24) and RORβ (Stehlin et al. (2001). X-ray structure of the orphan nuclear receptor RORbeta ligand-binding domain in the active conformation. EMBO J. 20(21), 5822-31; see Figures 6A and 6B). The most significant difference between FXR and other NHRs (RXR, VDR and PPARs) is in the replacement of the β-turn found following helix 5 with a more pronounced helix 6 (see Figure 6A). Also, the 15-residue insertion region between helices 1 and 3 is completely disordered in the FXR crystal structure (see Figures 6A and B). RXRα, which most closely resembles FXR in both primary sequence and length of the insertion region, has an additional helix (helix 2) in this position in the absence of ligand that unfolds upon binding of 9-*cis* retinoic acid (Egea et al. (2000, supra). This region of RXRα has been proposed to act as a "molecular spring" that accommodates the large conformational movements of helix 3 upon ligand binding. The insertion region may serve a similar role in hFXR, facilitating helix 3 rearrangements upon ligand binding. In the PPARs, this region contains a helix 2 and is the proposed ligand access site for the binding pocket. In SXR (Watkins et al (2001), supra) and VDR (Rochel et al. (2000). The Crystal Structure of the Nuclear Receptor for Vitamin D Bound to its Natural Ligand. Mol Cell 5, 173-179) the insertion domain region is significantly longer (see Figure 6B). Analysis of root mean square deviations (RMSD)

between the apo and ligand bound structures of SXR and VDR revealed no significant differences, suggesting that a shorter insertion domain region may be responsible for regulating large rearrangements of helix 3.

[0156] Significantly, the activation function-2 domain (AF2 or helix 12), essential for transcriptional activation of the receptor is packed against the body of FXR, positioned between helices 3 and 4 (see Figure 6A). This closed or active conformation is a signature feature that enables stable interactions between NHRs and their co-activator accessory protein partners (Xu et al. (2001), supra). By homology with NHR LBD structures, the LXXLL co-activator binding sequence would interact with the hydrophobic pocket formed between helices 3, 4, 5, and 12 that interacts with the hydrophobic face of the LXXLL helix located within co-activator proteins.

[0157] The ligand-binding cavity of the hFXR LBD is predominantly hydrophobic in nature and is formed by about 25 amino acids (see Figures 6C and 6D). The binding pocket has a volume of 726 A^3 which is smaller than that seen in SXR (1150 A^3) (Watkins et al. (2001), supra), but larger than that of RXRα (439 A^3) (Egea et al. (2000), supra; see Figure 6E). The fexaramine is sequestered between α helices 3 and 7 and makes significant contacts with helices 5, 6, 11 and 12 (see Figure 6B).

[0158] Interactions between FXR and fexaramine can be divided into two sets. The first set stabilizes the hexyl ring and the first benzene ring as well as the methyl ester moieties. The hexyl group makes minimal van der Waals contacts with Ile339 and Leu344 (helix 5), while Phe333 (helix 5) and Met369 and Phe370 (helix 7) create a hydrophobic surface behind fexaramine's central nitrogen and single benzyl group. Met294 (helix 3) as well as Leu352 and Ile356 (helix 6) stabilize the aliphatic linker between the first benzene ring and the methyl ester moiety (see Figure 6C). The methyl ester itself occupies a neutral groove between helices 3 and 6 and is stabilized by two hydrogen bonds from the NE2 proton of His298 (helix 3) and the hydroxyl of Ser336 (helix 5) to the amide carbonyl oxygen of fexaramine.

[0159] The second set of interactions stabilizes the biaryl rings and the dimethyl amine moiety. Phe288, Leu291, Thr292, and Ala295 (helix 3) form a hydrophobic surface on one side, while Ile361 (helix 6 and loop 7) and His451, Met454, Leu455, and Trp458 (helix 11)

form a hydrophobic surface on the other side of fexaramine's double ring structure. Phe465 (helix 11 and loop 12) and Leu469 and Trp473 (helix 12) bridge the hydrophobic surface from the helix 11 region to helix 3 creating a deep hydrophobic pocket that is filled by the biaryl moiety (see Figure 6E).

[0160] Thus, some combination of at least two of these amino acid residues in particular, and/or the structure coordinates corresponding thereto, can be used to define the points of interaction between a known or putative ligand or molecule capable of binding to FXR, and a FXR molecule.

[0161] The present invention provides novel chemical tools that activate FXR in a highly potent and specific fashion. Fexaramine was identified by utilization of a cell-based assay to screen a combinatorial library of approximately 10000 benzopyran compounds. The original compounds were discovered from the screen-activated FXR in the low μM range and were unique in chemical structure. Once discovered, these compounds were then systematically optimized to subsequently elucidate a high affinity agonist for FXR, termed fexaramine. The compound is chemically distinct from other synthetic and physiological agonists previously reported for FXR. Intensive structure activity analysis of this compound determined that the 3-methylcinnamate moiety in region I in addition to the cyclohexyl amide unit in region II are optimal for FXR agonist activity. Addition of a biaryl amine subunit at region III was necessary to achieve the maximal efficacy on FXR.

[0162] Characterization of fexaramine was undertaken and reported using both *in vitro* and *in vivo* assays. *In vitro* assays established that fexaramine and related ligands robustly recruited the co-activator SRC-1 peptide to FXR in a manner comparable to that of GW4064. Rigorous analysis of cell based in vivo assays with FXR response elements (ECRE and ER-8) and natural promoters of known target genes IBABP, PLTP and MRP-2 showed that these ligands could potently activate FXR in a concentration-dependent manner. When tested in cross reactivity experiments the fexaramine class of ligands showed no activity against a diverse range of other nuclear hormone receptors. Unlike the fexaramine class of compounds, GW4064 required the accessory protein RXR to achieve maximal efficacy in the chimeric GAL4DBD-FXR-LBD protein. This suggests that the *in vivo* binding of GW4064 to FXR may recognize the FXR/RXR heterodimer preferentially. Induction of known target

genes in both intestinal and liver cell systems demonstrated the usefulness of the identified compounds in studying FXR target genes. In intestinal cells treatment with fexaramine robustly induced the IBABP gene in a concentration dependent manner with efficacy similar to GW4064. Likewise, in the HEPG2 liver cell system, strong induction of target genes SHP, PLTP BSEP and MRP-2 was achieved at comparable concentrations of fexaramine and GW4064.

[0163] The specificity and efficacy of fexaramine allowed for a more detailed investigation of FXR target genes. Gene profiling of primary liver hepatocytes treated with three chemically distinct classes of FXR agonists revealed surprisingly little overlap. This exemplifies the difficulties of investigating NHR function using a ligand present at high physiological concentrations, and highlights the need for specific synthetic ligands. However, high affinity synthetic compounds tailored for the target protein may have non-specific effects on other pathways. This potential cross-reactivity may necessitate the development of multiple synthetic ligands to accurately discern receptor pathways and physiological relevance.

[0164] The crystal structure of FXR complexed with fexaramine allowed modeling of CDCA with a high degree of confidence into the ligand-binding pocket of FXR. This model provides a molecular explanation for the selectivity of BAs on FXR and highlighted the importance of position and orientation of the hydroxyl groups (position 7 and 3) in binding affinity. Specifically, this model provides a rationale for the beneficial effects of UDCA in the treatment of primary biliary cirrhosis. Although UDCA has two hydroxyl groups to potentially form hydrogen bonds with FXR in the ligand-binding cavity, their *trans* configuration create a more open ligand-binding pocket that would destabilize helix 12 and thereby inhibit activation of the receptor.

[0165] The present invention integrates chemical, genetic, and structural approaches to the analysis of FXR. In doing so, the present invention provides valuable and novel chemical tools to study the function of the receptor and also elucidates how FXR interacts with physiological natural and synthetic ligands at the molecular level.

[0166] The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLE 1

Identification and Development of Novel Small Molecule Ligands for FXR.

Expression and Reporter Constructs

[0167] The expression plasmids pCMX, pCMX-LacZ, pCMX-mFXRFL, pCMX-hRXRFL, pCMX-GALDBD-rFXRLBD and other pCMX-GALDBD-NR LBDs (hRXRα, hPPARαγδ, mPXR, hPXR, hLXRα, hTRβ, hRARβ, mCAR, mERR3 and hVDR) have been described elsewhere (Blumberg et al. (1998). SXR, a novel steroid and xenobiotic-sensing nuclear receptor. Genes Dev. 12(20), 3195-205). The reporter plasmids pMH2004-TK-luc, pTKECRE*6-luc, pTKER-8*2-luc and pMRP-2-luc also have been described elsewhere. The hPLTP-luc promoter was kindly provided by Dr Dennis Dowhan and the hIBABP-luc promoter was created from a plasmid provided by Dr Philippe Besnard.

[0168] Standard PCR amplifications of the LBD of human FXR (residues 248 to 476) and sub-cloning techniques were used to generate pGEX Glutathione-s-transferase (GST) and pHIS8-3 (Jez et al. (2000) Dissection of malonyl-coenzyme A decarboxylation from polyketide formation in the reaction mechanism of a plant polyketide synthase. Biochemistry 39, 890-902) prokaryote protein expression vectors. DNA fragments containing hFXR aa248 to 476 were cloned into the BamHI site of pGEX-hFXR, while the cloning sites NcoI and BamHI sites were used in pHIS8-3.

[0169] The retroviral plasmids were constructed by cloning FXRFL, FXR-AF2 and VP16-FXR cDNAs into the BamHI site of the established pBABE retroviral backbone vector. Viral extracts were established using published procedures and used to infect HT29 colon cells which, after exposure for 24 hours, were selected by addition of 4μg/ml of the drug puromycin. Cells that survived this selection procedure were then pooled and analyzed for the expression of the FXR gene.

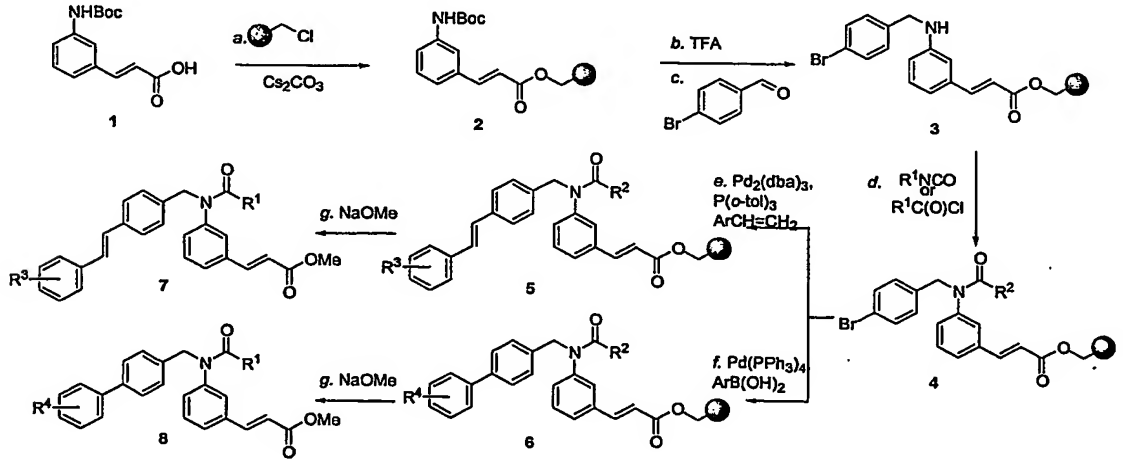
[0170] All constructs were verified by double-stranded sequencing to confirm identity and reading frame. Detailed information regarding each construct is available upon request.

[0171] For transfection of these constructs, monkey CV-1 HEPG2 and HEK293T cells were grown in DMEM supplemented with 10% FBS, 50 U/ml penicillin G, and 50 μg/ml

streptomycin sulfate at 37 °C in 7% CO2. CV-1 cells (60%-70% confluence, 48-well plate) were cotransfected with 16.6ng of the appropriate expression vector, 100 ng of reporter plasmid, and 100 ng of pCMX-LacZ in 200 µl of DMEM containing 10 % FBS by the N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium methylsulfate (DOTAP)-mediated procedure. After 24hr, the medium was replaced, and cells were harvested and assayed for luciferase activity 36-48hr after transfection. The luciferase activity was normalized to the level of β-galactosidase activity. Each transfection was performed in triplicate and repeated at least three times.

Solid Phase Synthesis of Small Molecule Ligands

[0172] The synthesis of this library was carried out on solid phase in a parallel fashion as summarized in the diagram below. Thus, Boc-protected cinnamic acid **1** was immobilized on Merrifield resin through the action of Cs_2CO_3 to afford conjugate **2**. The Boc group was removed from this resin by treatment with 20% TFA (for abbreviations see the legend of diagram below) in CH_2Cl_2 and the resultant resin-bound amine was reductively alklylated with 4-bromobenzaldehyde in the presence of $NaCNBH_3$ to yield amino resin **3**. Resin **3** was acylated with one of three acyl groups to give amide or urea resins **4**. The acylated resins (**4**) were then subjected to either a Heck coupling [$Pd_2(dba)_3$, P(*o*-tol)$_3$, Et_3N] with thirteen substituted styrenes or a Suzuki coupling [$Pd(PPh_3)_4$, Cs_2CO_3] with eighteen boronic acids to yield stilbene resins **5** and biaryl resins **6**, respectively. Cleavage of the resulting compounds from resins **5** and **6** with NaOMe yielded methyl cinnamates **7** and **8**. Analysis of the library by LCMS after purification showed the average purity of these compounds to be > 95%.



Solid phase synthesis of a 94-membered focused library of biaryl and stilbene cinnamates was as follows: Reagents and conditions: (a) 2.0 equiv of 3, 1.0 equiv of Merrifield Resin (0.91 mmol/g), 2.0 equiv of Cs_2CO_3, 0.5 equiv of TBAI, DMF, 55°C, 24 h; (b) 20% TFA in CH2Cl2, 25°C, 1 h; (c) 10.0 equiv of 4-bromobenzaldehyde, 0.05 equiv of AcOH, THF:MeOH (2:1), 25°C, 1 h; then, 8.0 equiv of NaCNBH3, THF:MeOH (2:1), 25°C, 2 h; (d) for R1COCl: 30.0 equiv of R1COCl, 40.0 equiv of Et3N, 1.0 equiv of 4-DMAP, CH2Cl2, 25°C, 12 h; for R^1NCO, 30.0 equiv of R1NCO, 40.0 equiv of Et3N, 1.0 equiv of 4-DMAP, DMF, 65°C, 60 h; (e) 8.0 equiv of styrene, 10.0 equiv of Et3N, 0.5 equiv of Pd2(dba)3,, 1.5 equiv of P(o-tol)3, DMF, 90°C, 48 h; (f) 5.0 equiv of boronic acid, 3.0 equiv Cs2CO3, 0.5 equiv of $Pd(PPh_3)_4$, DMF, 90°C, 24 h; (g) 10.0 equiv of NaOMe, Et2O:MeOH (10:1), 25°C, 20 min. AcOH = acetic acid; 4-DMAP=4-dimethylaminopyridine; DMF=N,N-dimethylformamide; Et=ethyl; Me=methyl; Pd(PPh3)4=tetrakis(triphenylphosphine)palladium(0); Pd2(dba)3=tris(dibezylideneacetone)dipalladium(0); P(o-tol)3=tri-o-tolylphosphine; TBAI=tetrabutylammonium iodide; TEA=triethylamine; TFA=trifluoroacetic acid; THF = tetrahydrofuran.

Screening for FXR Ligands

[0173] To discover novel small molecule ligands for FXR, a constructed combinatorial library of approximately 10 000 benzopyran compounds was screened using a cell-based assay in a 384 well format (Nicolaou et al. (2000). Natural product-like combinatorial libraries based on privileged structutres. 1. General principles and solid-phase synthesis of benzopyrans. J. Am. Chem. Soc. 122, 9939 – 9953; Natural product-like combinatorial libraries based on privileged structutres. 2. Construction of a 10000-membered benzopyran library by directed split-and-pool chemistry using nanokans and optical encoding. J. Am. Chem. Soc. 122, 9954 – 9967; and Natural product-like combinatorial libraries based on privileged structutres. 3. The "libraries from libraries" principle for diversity enhancement of benzopyran libraries. J. Am. Chem. Soc. 122, 9968 – 9976). This cell-based screen was based on the co-transfection of an expression vector containing the full-length FXR receptor with a reporter vector. The reporter vector contains a hormone response element under a minimal eukaryotic promoter driving a luciferase reporter gene. The initial screen identified several lead compounds, possessing activities ranging from 5 – 10 μM and whose prototypical structure (1) is shown in Figure 1A. Lead compounds were re-tested and

checked for cross-reactivity for the retinoid X receptor (RXR), the heterodimeric partner of FXR. None of the identified compounds had the ability to bind or activate RXR.

[0174] Systematic optimization of regions I and II of the prototypical structure through multiple rounds of screening using smaller "focused" chemical libraries defined the requisite features of these domains for high affinity binding to FXR. Specifically, incorporation of the 3-methylcinnamate moiety in region I and the cyclohexyl amide unit in region II resulted in a more than 10-fold enhancement in the potency, as demonstrated by compound **2** (EC_{50} = 358 nM) (Figure 1A). Preliminary exploration of region III suggested that replacement of the parent benzopyran unit with styrenyl and biaryl moieties within this latter scaffold (**2**) would yield compounds with even higher potency. This intelligence gathering was then used to design and synthesize on a solid support a focused library of 94 new compounds for further optimization.

[0175] Screening of the synthesized compound library led to the discovery of several highly potent ligands including (see Figure 1); **A** [coined fexaramine: EC_{50} = 25 nM], **B** [coined fexarine: EC_{50} = 38 nM] and **C** [coined fexarene: EC_{50} = 36 nM], as well as many lower affinity compounds such as **D** [coined SRI-1: EC_{50} = 377 nM] and **E** [coined SRI-2: EC_{50} = 343 nM], the structures of which are shown in Figure 1B. Furthermore, these compounds are structurally distinct from the known natural and synthetic ligands for FXR; the BA chenodeoxycholic acid (CDCA) and GW4064 shown in Figure 1B **F** and **G**. GW4064 exhibited EC_{50} values of approximately 90 nM, comparable to the known values.

EXAMPLE 2

Activation of FXR by Novel Compounds

[0176] To determine if the compounds identified as ligands could promote the association of FXR with co-activators *in vitro*, a fluorescence resonance energy transfer (FRET)-based coactivator binding assay was employed (see, for example, Makishima et al. (1999), supra; Urizar et al. (2002). A natural product that lowers cholesterol as an antagonist ligand for FXR. Science. 296(5573), 1703-6). This assay relies on an agonist-induced interaction between the nuclear receptor and its coactivator bringing two fluorogenic partners together resulting in the nuclear receptor ligand-dependent FRET. Specific

recruitment of a peptide containing the receptor binding domain of the steroid receptor co-activator SRC-1 (LXXLL) to the FXR ligand-binding domain was only observed in the presence of the agonists fexaramine, fexarine, fexarene, SRI-1, SRI-2 and GW4064 (see Figure 1C). GW4064 demonstrated the strongest recruitment with an EC_{50} value of 100nM followed by fexaramine (EC_{50} 255nM), fexarine (EC_{50} 222nM), and fexarene (EC_{50} ≈255nM). Weaker recruitment is seen with compounds SRI-1 and SRI-2.

[0177] The ability of these compounds to activate the receptor in a number of different cell-based reporter gene assays was then determined. The recently identified high affinity non-steroidal synthetic compound GW4064 was used as a control in these experiments. CV-1 cells were transiently transfected with an expression plasmid for mouse FXR and human RXR with a thymidine kinase (TK) minimal promoter reporter vector containing either no copies or six copies of the ecdysone response element (ECRE), a well-characterized FXR response element (FXRE). In addition, two copies of the recently identified FXRE everted repeat separated by 8 nucleotides (ER-8) was also studied (see, for example, Laffitte et al. (2000). Identification of the DNA binding specificity and potential target genes for the farnesoid X-activated receptor. J Biol Chem. 275(14), 10638-47; Kast et al. (2002). Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. J Biol Chem. 277(4), 2908-15).

[0178] The cells were then treated with increasing concentrations of fexaramine, fexarine, fexarene, SRI-1, SRI-2 or GW4064. The results depicted in Figures 2B and C show that fexaramine, fexarine, fexarene and GW4064 showed robust activation of both of the FXREs (ECRE 100-fold; ER-8 4-fold) with a maximal activity achieved at 1 μM (concentrations higher than 1 μM were tested but produced no more activity). The compounds SRI-1 and SRI-2, although structurally similar to fexaramine, showed little or no activity. Novel compounds idntified above showed no activity on the minimal TK promoter. However, GW4064 displayed a weak activity (less than 2 fold) on this promoter (see Figure 2A). Similar results were found in a variety of different cell types including liver cells (HEPG2) and kidney cells (HEK 293).

[0179] Having demonstrated that the newly identified compounds could robustly activate multiple copies of FXREs linked to a TK minimal promoter , the ability of the compounds to activate natural promoters of known FXR targets in a transient transfection cell-based assay was examined. For this study, the following gene promoters were used: intestinal bile acid binding protein (IBABP; see, for example, Grober et al. (1999). Identification of a bile acid-responsive element in the human ileal bile acid-binding protein gene. Involvement of the farnesoid X receptor/9-cis-retinoic acid receptor heterodimer. J Biol Chem. 274(42), 29749-54), phospholipid transfer protein (PLTP) (Urizar et al (2000). The farnesoid X-activated receptor mediates bile acid activation of phospholipid transfer protein gene expression. J Biol Chem. 275(50), 39313-7) and multidrug resistance related protein 2 (MRP-2) (Kast et al. (2002), supra), which are all well characterized targets of FXR. The natural promoters of both the IBABP and PLTP genes contain one copy of an inverted repeat with a one base spacing (IR-1) while MRP-2 contains an ER-8 element. The results obtained, shown in Figures 2 D (hIBABP promoter), 2E (hPLTP promoter) and 2F (hMRP-2 promoter), were similar to experiments with multiple FXRE copies with maximium efficacy of the fexaramine, fexarine, fexarene and GW4064 compounds observed at 1 μM, while SRI-1 and SRI-2 showed little or no activity. The most robust activation (28-fold) was seen on the IBABP promoter. Less robust (2-3 fold) but specific activation was observed on the PLTP and MRP-2 promoters.

EXAMPLE 3

Cross reactivity of FXR Ligands with other Nuclear Receptors

[0180] Cell-based transcriptional activation assays using chimeric nuclear hormone receptor (NHR) constructs were established to measure the selectivity of the compounds to FXR relative to other NHRs (Forman et al. (1995). Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 81, 687–693). These assays used fusion proteins with the yeast GAL4 DNA binding domain connected to the ligand-binding domain (LBD) of NHRs. These constructs were co-transfected with a thymidine kinase (TK) minimal promoter reporter vector containing four copies of the GAL4 binding site. Titration experiments were then performed using the identified compounds. Figures 3A and 3B show that fexaramine, fexarine, fexarene and GW4064 all activate the chimeric FXR construct in the presence and absence of RXR. Interestingly, fexaramine, fexarine, fexarene are more

efficacious ligands for FXR than GW4064 in the absence of RXR suggesting some difference between the mechanism of activation between the two classes of compounds. Addition of RXR had no effect on the activation potential of fexaramine, fexarine, fexarene in this assay. Compounds SRI-1 and SRI-2 again showed little or no activity consistent with previous results.

[0181] In this assay fexaramine, fexarine and fexarene were highly selective for FXR. No activity was observed on other chimeric NHR constructs including hRXRα, hPPARαγδ, mPXR, hPXR, hLXRα, hTRβ, hRARβ, mCAR, mERR3 and hVDR (see Figures 3C - 3E).

EXAMPLE 4

Induction of FXR Target Genes by Novel Compounds

RNA Isolation and Northern Blot Hybridization

[0182] HepG2 or HT29-derived cell lines were typically cultured in medium containing superstripped FBS for 24hr before the addition of a ligand or DMSO (vehicle) for an additional 24-48hr. Total RNA was isolated using TRIzol reagent and was resolved (10 μg/lane) on a 1% agarose, 2.2 M formaldehyde gel, transferred to a nylon membrane (Hybond N+; Amersham Biosciences, Inc.), and cross-linked to the membrane with UV light.

[0183] cDNA probes were radiolabeled with [α-^{32}P]dCTP using the highprime labeling kit (Amersham Biosciences, Inc.). Membranes were hybridized using the QuikHyb hybridization solution (Stratagene, La Jolla, CA) according to the manufacturer's protocol. Blots were normalized for variations of RNA loading by hybridization to a control probe, either, 18 S ribosomal cDNA, or the ribosomal protein 36B4. The RNA levels were quantitated using a PhosphorImager (ImageQuant software; Molecular Dynamics, Inc., Sunnyvale, CA) in addition to being exposed to X-ray film.

RNA Analysis of FXR Target Genes

[0184] The liver and the intestinal system are the major areas where FXR plays a role in the induction of specific gene targets in response to bile acid (BA) concentrations. To establish that the identified compounds are effective in studying the function of FXR in these systems, the compounds were examined for their ability to induce characterized gene

targets. In addition to the ability to induce characterized gene targets, invention compounds are also useful for identification of gene targets for FXR, i.e., genes which are modulated (i.e., induced or repressed) by FXR.

[0185] Human colon cells HT29 (FXR null until differentiated) were infected with retroviral vectors that expressed either FXR constructs and the puromycin-resistant gene or the puromycin-resistant gene alone. Puromycin resistant cells were isolated and pooled cell populations were propagated that harbored either the vector alone (HT29-BABE), overexpressed FXR full length (HT29-FXRFL), a non-functional FXR truncated at the AF2 region (HT29-FXR-AF2), or a constitutively active FXR that has the VP16 activation domain fused N-terminal of the protein (HT29-VP16-FXR). Confirmation of the successful establishment of the different stable cell lines was established via northern blot analysis of FXR message levels in the cells (see Figure 4A).

[0186] HT29-BABE lines do not express FXR while the stable cell lines expressed the exogenous FXR message. To test the ability of these cell lines to induce FXR target genes total RNA was isolated from cells treated overnight with increasing amounts of CDCA or GW4064. Northern blot analysis of the HT29-FXRFL cell line showed robust concentration dependent induction of IBABP mRNA by both CDCA and GW4064 (see Figures 4B and 4C). Maximal activation of the IBABP gene by CDCA was observed at 100 μM while only 1 μM of GW4064 was needed to achieve the same level of induction. No induction of IBABP mRNA levels was observed in the HT29-BABE or HT29-FXR-AF2 cell lines. Constitutive expression was seen in the HT29-VP16-FXR and was super-induced by addition of CDCA and GW4064. These observations verify the usefulness of this colon cell model system for studying the induction of FXR target genes.

[0187] The ability of the novel compounds identified herein to induce IBABP gene expression in this cell system was also examined. Total RNA from HT29 stable cells treated overnight with fexaramine, fexarine and fexarene was probed for IBABP gene expression (see Figure 4D). Fexaramine, fexarine and fexarene all induced expression of the IBABP mRNA in the HT29-FXRFL with similar profiles to that seen for GW4064 (maximal activity at 1 μM concentration). No induction was seen in the HT29-BABE or HT29-FXR-AF2 cell lines, proving the specificity of the compounds. These results demonstrate that the novel

compounds of the present invention are effective in studying FXR target genes in an intestinal model cell system.

[0188] To demonstrate the usefulness of these compounds in studying FXR function in the liver, a model hepatocyte cell system that expresses the FXR gene was employed (Kast et al. (2002), supra). Confluent HEPG2-FXR cells were treated overnight with increasing concentrations of fexaramine, fexarine, fexarene SRI-1, SRI-2 and the control ligands GW4064 and CDCA. Total RNA was isolated and the expression of the FXR target genes SHP, MRP-2, BSEP and PLTP was measured by Northern blot analysis (see Figure 4E).

[0189] The control ligands CDCA and GW4064 showed similar induction of the target genes to what has been previously reported. Of the novel compounds identified herein, fexaramine was the most effective inducer of target genes, although strong induction was also observed with fexarine and fexarene. In this hepatocyte cell system, maximal activation of FXR target genes by these compounds was achieved at 10 μM, which is similar to the control ligand GW4064. Interestingly, although GW4064 showed slightly better induction of the FXR target genes PLTP and SHP, fexaramine matched GW4064 induced activation of the BSEP and MRP-2 genes. These results demonstrate that these novel compounds can be used to identify and characterize new FXR target genes in the liver and the intestinal cell systems. Differences in efficacy of target gene induction between the liver and the intestinal cell systems may reflect the ability of the liver hepatocytes to mount a xenobotic response or cell specific permeability to the identified compounds. Modification of the ligands to overcome these effects may be made in order to increase the efficacy of these drugs in liver cell systems.

[0190] Further evidence that invention compounds can be used to identify and characterize additional FXR gene targets is provided by the large scale screening summarized in Appendix 2 (for genes upregulated by invention compounds) and Appendix 3 (for genes downregulated by invention compounds).

EXAMPLE 5

Gene Profiling of FXR Agonists

[0191] Having established fexaramine as a potent FXR specific agonist in two model cell systems, its gene activation profile with CDCA and GW4064 in human primary hepatocytes was then compared. Hepatocytes were treated with DMSO (control group), fexaramine (10 μM), CDCA (100 μM), or GW4064 (10 μM) and total RNA isolated at 6 and 12-hour time points. Prior to gene profiling experiments the samples were verified by Northern blot analysis for induction of a known FXR target gene SHP (see Figure 5A). Subsequently, biotinylated cRNAs prepared from mRNA samples were hybridized to duplicate sets of high-density microarrays (U-133A set Affymetrix, Palo Alto, CA) to minimize experimental error.

[0192] A total of 222 transcripts were identified whose expression changed with respect to DMSO using a paired student's T-test. These genes were then subjected to hierarchal clustering and visualized using the Treeview. The most striking observation was the very unique profiles seen by the different FXR agonists (see Figure 5B). Relatively few genes were observed whose expression changed with all three agonists. This may, in part, be due to CDCA regulating genes via non-FXR pathways. The recent body of work by Wang et al supports this idea, which demonstrated that BAs mediate repression of the CYP7A in a SHP independent manner through the activation of the xenobiotic receptor PXR or the c-Jun N-terminal kinase JNK (Wang et al. (2002), supra).

[0193] In addition, a small subset of genes (see Figure 5C) were changed over 3-fold by all three FXR ligands. The largest change was seen in the apolipoprotein E gene repression. This result correlates with levels observed in *FXR* null mice where increases in apoE levels in the VLDL, LDL, and HDL fractions were seen when compared with wild-type mice (Sinal et al. (2000), supra). This list suggests additional roles for FXR in the bilirubin biosynthetic pathway (BLVRA 5-fold), thyroid metabolism (TSHR 3-fold; thyroid transcription factor 1 3-fold) and amino acid transport (SCL7A2 4-fold), as well as other pathways (see also Appendix 2 and Appendix 3). Confirmation of gene induction by FXR agonists of many of the genes reported in this list have been checked by Northern blot analysis as well.

EXAMPLE 6

Crystallographic Elucidation of FXR Structure

[0194] The plasmids pGEX or pHIS8-3-hFXR LBD (residues 248 to 476 of SEQ ID NO:1) were transformed into *E. coli* strain BL21 (DE3) (Novagen) and cells were grown at 37 °C to an $O.D._{600}$ of 1.0. Protein expression was induced by adding iso-propyl-*thio*-galactose (Boehringer Mannheim) at a concentration of 0.1 mM and cells were allowed to grow for 6 hr at 20 °C. Bacteria were harvested at 8,000 x g at 5 °C and pellets were stored at -70 °C. Cell pellets were thawed and resuspended in 50 mM Tris-Cl (pH 8.0), 500 mM NaCl, 10 mM imidazole (pH 8.0), 10% glycerol, 1% Tween 20, and 10 mM β-mercaptoethanol (β-ME) (Sigma) at 4 °C.

[0195] Resuspended cells were sonicated and lysates were centrifuged at 100,000 x g at 4 °C. Supernatants were purified by Ni^{2+}-chelation chromatography (QIAGEN). Protein sample was eluted in 50 mM Tris-Cl (pH 8.0), 500 mM NaCl, 250 mM imidazole (pH 8.0), 10% glycerol, and 10 mM β-ME. The N-terminal octahistidine tag was removed by thrombin (Sigma) digestion during dialysis against 50 mM Tris (pH 8.0), 500 mM NaCl, and 10 mM dithiotheitol (DTT) at 4 °C for 24 h. The sample was purified over Superdex 200 26/60 gel filtration column (Pharmacia) equilibrated in dialysis/thrombin cleavage buffer. Peak fractions were collected and dialyzed against 5 mM Tris (pH 8.0) 62.5 mM NaCl and 1 mM DTT, concentrated to 15 mg ml^{-1} using Centricon 10 (Amicon), and stored at - 70°C. Selenomethionine substituted protein (SeMet) was obtained from *E. coli* grown in minimal media using the methionine pathway inhibition methods (Doublié (1997). Preparation of selenomethionyl proteins for phase determination. Methods Enzymol. 276, 523-530) and was purified similarly to the native sample.

Crystallization and Structure Determination

[0196] Complexing of the receptor with the ligand was accomplished by incubating hFXR (15 mg ml^{-1}) with fexaramine at a 1:2 molar ratio. Fexaramine was solubilized in dimethylsulfoxide (DMSO) at 10 mM. Crystals of the hFXR-LBD with fexaramine were grown by the hanging drop vapor diffusion methods at 4 °C by mixing 1.0 µl of hFXR-LBD/fexaramine complex with 1.0 µl of a reservoir solution containing 15%-20% PEG 8000, 100 mM HEPES-Na^+ (pH 7.5), 0.2 M $MgCl_2$, 1 mM DTT. Crystals of selenomethionine-

substituted hFXR-LBD were grown similarly with an increase in DTT concentration to 10 mM. Crystals were stabilized in 10%-15% glycerol, 20% PEG 8000, 0.2 M $MgCl_2$, 100 mM HEPES-Na^+ (pH 7.5), and 10 mM DTT and rapidly frozen in a 100K stream of nitrogen gas.

[0197] MAD data to 2.1 Å was collected around the Se edge at European Synchrotron Radiation Facility (ESRF, Grenoble, France) on beamline FIP (BM30A). Native data to 1.78 Å was collected at the Stanford Synchrotron Radiation Laboratory, beamline 9-1. All data was processed with DENZO and SCALEPACK (Otwinowski and Minor (1997). Processing of X-ray diffraction data collected in oscillation mode. Methods Enzymol. 276, 307-326). The crystals contain one molecule per asymmetric unit (52.9% solvent) and belong to the space group $P2_12_12_1$ (a=36.656, b=56.776, c=117.646, α=90.0, β=90.0, γ=90.0). Three wavelength MAD data were scaled to the λ_3 and verified by inspection of both dispersive and anomalous difference. 7 of 9 Se sites were located and MAD phasing was done with SOLVE (Terwilliger and Berendzen (1992). Automated MAD and MIR structure solution. Acta Crystallogr. D 55, 849-861.) and density modification was carried out with RESOLVE (Terwilliger (2000) "Maximum likelihood density modification," Acta Cryst. D56, 965-972).

[0198] The initial model was built into the experimental electron density maps displayed in O (Jones et al. (1991) Improved methods for building protein models in electron density maps and the location of errors in these models. Acta Crystallogr. A 47, 110-119). The resulting model was positionally refined against all the high-resolution native data set using the default bulk solvent model in CNS with maximum likelihood targets (Brunger et al. (1998). Crystallography & NMR system: A new software suite for macromolecular structure determination. Acta Crystallogr. D 54, 905-921). The structure of FXR was refined to a R_{cryst} and a R_{free} value of 23.0% and 27.5%, using all data extending to 1.78 Å resolution. The R-factor = $\sum | F_{obs} - F_{calc} | \; / \; \sum_{Fobs}$, where summation is over the data used for refinement and the R_{free} was calculated using 5% of the reflection data chosen and excluded from refinement. The model consists of residues 248 to 270 and 286 to 475 of human FXR, 1 fexaramine molecule, and 340 water molecules. PROCHECK (Laskowski et al. (1993). PROCHECK: a program to check the stereochemical quality of protein structures. J. Appl. Crystallogr. 26, 283-291) revealed a total of 92% of the residues in the most favored region of the Ramachandran plot and 8% in the additionally allowed region. Main chain and side chain structural parameters were consistently better than average (overall G value of 0.16).

EXAMPLE 7

Modeling Compounds into the FXR LBD Crystallographic Structure

[0199] The structure of the activated form of the FXR LBD allowed investigation of how BAs, structurally distinct physiological ligands for FXR, bind and activate the receptor. The bile acid CDCA was initially modeled into the FXR binding pocket by overlaying its steroidal backbone onto the biaryl group in fexaramine (see Figure 6E). The model suggested that potential hydrogen bonds could occur between CDCA's hydroxyl groups and Tyr365, Tyr373, and His451 in helices 7 and 11. These interactions were subsequently used to refine the modeled orientation of the ligand. In this model, hydrophobic interactions with CDCA are predicted to secure helix 3 in a similar orientation to that seen in the complex with fexaramine.

[0200] This model also provides an explanation for the partial activation of FXR by lithocholic acid (LCA) and deoxycholic acid (DCA) (Makishima et al. (1999), supra). These BAs lack one of the two hydroxyl groups (the αOH at position 7) found in CDCA and therefore are predicted to interact significantly only with the helix 7. These BAs would therefore not bridge helix 3 to helix 7 as securely as CDCA, which in turn, would affect the rigidity of helix 12. In addition, although the inhibitory BA ursodeoxycholic acid (UDCA) has two hydroxyl groups, their *trans* rather than *cis* relationship would orientate UDCA in a manner that would create a more open ligand-binding pocket. This in turn may force a less than optimal orientation of helix 12 and result in inhibition of the co-activator interaction.

[0201] Modeling of the recently identified synthetic BA agonist 6alpha-ethyl-chenodeoxycholic acid 6-ECDCA, onto the positional coordinates for the CDCA model further supports the model and suggests a mechanism for its efficacy (Pellicciari et al. (2002). 6-alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 45(17), 3569-72). 6-ECDCA differs from CDCA by an addition of an aliphatic moiety at the 6α position. The ethyl substituent at this position would be predicted to fit snugly into a hydrophobic pocket formed by Met332 and Phe333 from helix 5. Furthermore, it was demonstrated that either a methyl substituent or a bulkier group at this position reduced efficacy (Pellicciari et al. (2002), supra). This model would predict that a methyl substituent would not be not as effective as an ethyl group because it does not fill the hydrophobic pocket as well as the ethyl group and therefore

would not maximize binding energy through an increase in contact surface resulting in a loss of efficacy. Bulkier substituents would also be unfavorable, as they would surpass the 0.3 Å limit allowed for in overlap before Van der Waals contacts would become energetically unfavorable.

[0202] Fexaramine is a much stronger activator of FXR than even its most potent natural ligand. This potency appears to be mediated by two mechanisms. First, the fexaramine methyl ester group provides a significant number of contacts with helix 3 that are absent in our model of CDCA binding. The methyl ester aliphatic chain effectively bridges helix 3 with helix 6 through van der Waals contacts. FXR further stabilizes helix 3 against the remainder of the structure via interactions between Asn297 from helix 3 and Arg335 from helix 5, in addition to interactions from Asn286 (helix 3) and Arg354 from helix 6. The second mechanism seems to be a function of fexaramine's length. Fexaramine and compounds of similar length such as fexarene and fexarine activate FXR at much lower concentrations than the natural ligands. It appears that the sequential hydrophobic ring structures of these compounds penetrate deeper into the ligand-binding pocket and thereby increase the number of stable contacts. The larger size of fexaramine compared to CDCA (fexaramine has a volume of 461 $Å^3$ and a surface area of 465 $Å^2$; CDCA has a volume of 339 $Å^3$, and a surface area of 319 $Å^2$), more effectively fills the ligand-binding cavity. Analysis of buried surface area in the absence and presence of fexaramine reveals an additional 9 $Å^2$ of buried hydrophobic surface when fexaramine is bound. This corresponds to an increase of approximately 1 kJ/M in stabilizing energy. Fexaramine also appears to make direct contact with helix 12 as well. The increase in stabilization of helix 12 directly influences its rigidity and hence its ability to interact with the co-activator.

[0203] While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements should be apparent without departing from the spirit and scope of the invention. The present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The examples provided here are representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Modifications therein and other uses will occur to

those skilled in the art. These modifications are encompassed within the spirit of the invention and are defined by the scope of the claims.

[0204] The disclosure of all publications cited above are expressly incorporated herein by reference, each in its entirety, to the same extent as if each were incorporated by reference individually.

APPENDIX 1

STRUCTURE COORDINATES FOR FXR LBD COMPLEXED WITH FEXARAMINE

```
REMARK Written by O version 6.1.0
REMARK Thu Oct 10 10:35:28 2002
CRYST1   36.656   56.776  117.646  90.00  90.00  90.00
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.027281 -0.000001 -0.000001        0.00000
SCALE2      0.000000  0.017613  0.000000        0.00000
SCALE3      0.000000  0.000000  0.008500        0.00000
```

ATOM	#	TYPE	RESIDUE		X	Y	Z	OCC	B	
ATOM	1	N	GLU	248	-1.300	16.662	18.408	1.00	26.06	7
ATOM	2	CA	GLU	248	0.018	16.006	18.347	1.00	24.32	6
ATOM	3	CB	GLU	248	1.089	16.982	18.816	1.00	23.43	6
ATOM	4	CG	GLU	248	1.214	18.242	17.971	1.00	26.14	6
ATOM	5	CD	GLU	248	0.206	19.376	18.316	1.00	26.65	6
ATOM	6	OE1	GLU	248	-0.853	19.163	18.951	1.00	26.91	8
ATOM	7	OE2	GLU	248	0.471	20.527	17.904	1.00	28.84	8
ATOM	8	C	GLU	248	0.066	14.789	19.297	1.00	23.85	6
ATOM	9	O	GLU	248	0.952	13.973	19.208	1.00	22.37	8
ATOM	10	N	LEU	249	-0.854	14.728	20.262	1.00	22.87	7
ATOM	11	CA	LEU	249	-0.844	13.653	21.236	1.00	22.90	6
ATOM	12	CB	LEU	249	-1.530	14.121	22.530	1.00	23.10	6
ATOM	13	CG	LEU	249	-0.943	15.332	23.292	1.00	23.04	6
ATOM	14	CD1	LEU	249	-1.713	15.572	24.612	1.00	18.74	6
ATOM	15	CD2	LEU	249	0.552	15.118	23.434	1.00	22.62	6
ATOM	16	C	LEU	249	-1.679	12.497	20.693	1.00	23.78	6
ATOM	17	O	LEU	249	-2.675	12.765	20.060	1.00	22.65	8
ATOM	18	N	THR	250	-1.294	11.253	20.952	1.00	21.78	7
ATOM	19	CA	THR	250	-2.131	10.116	20.532	1.00	21.44	6
ATOM	20	CB	THR	250	-1.465	8.742	20.857	1.00	18.84	6
ATOM	21	OG1	THR	250	-1.263	8.652	22.258	1.00	19.62	8
ATOM	22	CG2	THR	250	-0.098	8.627	20.156	1.00	19.88	6
ATOM	23	C	THR	250	-3.430	10.156	21.387	1.00	22.71	6
ATOM	24	O	THR	250	-3.542	10.917	22.374	1.00	20.79	8
ATOM	25	N	PRO	251	-4.420	9.330	21.006	1.00	21.51	7
ATOM	26	CD	PRO	251	-4.608	8.786	19.642	1.00	22.74	6
ATOM	27	CA	PRO	251	-5.670	9.278	21.766	1.00	23.11	6
ATOM	28	CB	PRO	251	-6.493	8.238	20.996	1.00	20.67	6
ATOM	29	CG	PRO	251	-6.160	8.602	19.547	1.00	20.95	6
ATOM	30	C	PRO	251	-5.380	8.870	23.189	1.00	23.37	6
ATOM	31	O	PRO	251	-5.977	9.431	24.134	1.00	23.44	8
ATOM	32	N	ASP	252	-4.424	7.940	23.375	1.00	22.26	7
ATOM	33	CA	ASP	252	-4.108	7.483	24.716	1.00	22.24	6
ATOM	34	CB	ASP	252	-3.009	6.414	24.756	1.00	24.95	6
ATOM	35	CG	ASP	252	-3.530	4.944	24.647	1.00	27.66	6
ATOM	36	OD1	ASP	252	-2.631	4.061	24.671	1.00	29.71	8
ATOM	37	OD2	ASP	252	-4.769	4.666	24.531	1.00	25.30	8
ATOM	38	C	ASP	252	-3.571	8.679	25.555	1.00	21.99	6
ATOM	39	O	ASP	252	-3.937	8.824	26.712	1.00	21.47	8
ATOM	40	N	GLN	253	-2.677	9.453	24.971	1.00	19.91	7

```
ATOM     41  CA  GLN   253      -2.050  10.588  25.632  1.00 20.91   6
ATOM     42  CB  GLN   253      -0.894  11.111  24.764  1.00 18.51   6
ATOM     43  CG  GLN   253       0.265  10.122  24.650  1.00 20.05   6
ATOM     44  CD  GLN   253       1.382  10.622  23.735  1.00 21.33   6
ATOM     45  OE1 GLN   253       1.105  11.105  22.638  1.00 18.67   8
ATOM     46  NE2 GLN   253       2.640  10.535  24.126  1.00 20.72   7
ATOM     47  C   GLN   253      -3.049  11.692  25.938  1.00 21.83   6
ATOM     48  O   GLN   253      -2.956  12.372  26.972  1.00 20.56   8
ATOM     49  N   GLN   254      -3.987  11.862  25.047  1.00 20.43   7
ATOM     50  CA  GLN   254      -5.019  12.868  25.236  1.00 22.66   6
ATOM     51  CB  GLN   254      -5.973  12.874  24.057  1.00 24.24   6
ATOM     52  CG  GLN   254      -5.363  13.502  22.811  1.00 25.78   6
ATOM     53  CD  GLN   254      -6.374  13.651  21.684  1.00 28.28   6
ATOM     54  OE1 GLN   254      -7.373  12.935  21.661  1.00 31.15   8
ATOM     55  NE2 GLN   254      -6.172  14.547  20.740  1.00 27.90   7
ATOM     56  C   GLN   254      -5.789  12.561  26.519  1.00 25.16   6
ATOM     57  O   GLN   254      -6.045  13.443  27.339  1.00 26.26   8
ATOM     58  N   THR   255      -6.152  11.297  26.697  1.00 23.88   7
ATOM     59  CA  THR   255      -6.930  10.897  27.888  1.00 25.99   6
ATOM     60  CB  THR   255      -7.467   9.474  27.762  1.00 27.10   6
ATOM     61  OG1 THR   255      -6.402   8.543  27.765  1.00 33.09   8
ATOM     62  CG2 THR   255      -8.276   9.258  26.486  1.00 22.32   6
ATOM     63  C   THR   255      -6.077  11.004  29.160  1.00 25.75   6
ATOM     64  O   THR   255      -6.566  11.405  30.223  1.00 25.60   8
ATOM     65  N   LEU   256      -4.820  10.634  29.028  1.00 24.61   7
ATOM     66  CA  LEU   256      -3.852  10.712  30.136  1.00 25.14   6
ATOM     67  CB  LEU   256      -2.473  10.285  29.614  1.00 29.20   6
ATOM     68  CG  LEU   256      -1.584   9.546  30.626  1.00 34.14   6
ATOM     69  CD1 LEU   256      -2.275   8.363  31.302  1.00 33.98   6
ATOM     70  CD2 LEU   256      -0.317   8.968  29.977  1.00 34.33   6
ATOM     71  C   LEU   256      -3.793  12.167  30.644  1.00 24.91   6
ATOM     72  O   LEU   256      -3.933  12.449  31.843  1.00 24.12   8
ATOM     73  N   LEU   257      -3.593  13.073  29.698  1.00 22.63   7
ATOM     74  CA  LEU   257      -3.489  14.513  29.987  1.00 21.99   6
ATOM     75  CB  LEU   257      -3.157  15.292  28.719  1.00 19.83   6
ATOM     76  CG  LEU   257      -3.122  16.802  28.945  1.00 22.40   6
ATOM     77  CD1 LEU   257      -2.121  17.218  30.025  1.00 18.07   6
ATOM     78  CD2 LEU   257      -2.738  17.577  27.683  1.00 21.13   6
ATOM     79  C   LEU   257      -4.808  15.056  30.543  1.00 21.92   6
ATOM     80  O   LEU   257      -4.824  15.859  31.487  1.00 20.03   8
ATOM     81  N   HIS   258      -5.892  14.607  29.942  1.00 23.40   7
ATOM     82  CA  HIS   258      -7.237  15.040  30.339  1.00 25.69   6
ATOM     83  CB  HIS   258      -8.314  14.293  29.553  1.00 29.97   6
ATOM     84  CG  HIS   258      -9.707  14.478  30.162  1.00 33.41   6
ATOM     85  CD2 HIS   258     -10.443  13.693  30.993  1.00 34.61   6
ATOM     86  ND1 HIS   258     -10.480  15.610  29.914  1.00 32.40   7
ATOM     87  CE1 HIS   258     -11.616  15.487  30.579  1.00 35.27   6
ATOM     88  NE2 HIS   258     -11.609  14.350  31.228  1.00 34.65   7
ATOM     89  C   HIS   258      -7.482  14.790  31.836  1.00 26.38   6
ATOM     90  O   HIS   258      -7.865  15.691  32.589  1.00 25.22   8
ATOM     91  N   PHE   259      -7.261  13.566  32.284  1.00 26.46   7
ATOM     92  CA  PHE   259      -7.528  13.226  33.694  1.00 28.16   6
ATOM     93  CB  PHE   259      -7.498  11.716  33.905  1.00 30.66   6
ATOM     94  CG  PHE   259      -8.829  11.079  33.506  1.00 34.91   6
ATOM     95  CD1 PHE   259     -10.023  11.523  34.094  1.00 36.00   6
ATOM     96  CD2 PHE   259      -8.860  10.065  32.544  1.00 37.80   6
ATOM     97  CE1 PHE   259     -11.247  10.966  33.700  1.00 37.55   6
ATOM     98  CE2 PHE   259     -10.084   9.514  32.144  1.00 38.35   6
```

ATOM	99	CZ	PHE	259	-11.278	9.966	32.720	1.00 38.15	6
ATOM	100	C	PHE	259	-6.539	13.924	34.627	1.00 27.70	6
ATOM	101	O	PHE	259	-6.864	14.275	35.770	1.00 27.66	8
ATOM	102	N	ILE	260	-5.330	14.140	34.156	1.00 23.14	7
ATOM	103	CA	ILE	260	-4.344	14.817	34.994	1.00 23.49	6
ATOM	104	CB	ILE	260	-2.948	14.774	34.372	1.00 23.27	6
ATOM	105	CG2	ILE	260	-2.001	15.819	34.986	1.00 22.34	6
ATOM	106	CG1	ILE	260	-2.284	13.406	34.577	1.00 21.63	6
ATOM	107	CD1	ILE	260	-0.954	13.251	33.849	1.00 24.51	6
ATOM	108	C	ILE	260	-4.798	16.258	35.233	1.00 21.79	6
ATOM	109	O	ILE	260	-4.790	16.750	36.366	1.00 20.94	8
ATOM	110	N	MET	261	-5.212	16.907	34.164	1.00 20.87	7
ATOM	111	CA	MET	261	-5.652	18.308	34.232	1.00 23.03	6
ATOM	112	CB	MET	261	-5.854	18.867	32.830	1.00 22.66	6
ATOM	113	CG	MET	261	-4.551	18.918	32.028	1.00 22.62	6
ATOM	114	SD	MET	261	-3.187	19.588	32.956	1.00 21.46	16
ATOM	115	CE	MET	261	-3.583	21.246	33.464	1.00 19.31	6
ATOM	116	C	MET	261	-6.954	18.440	35.030	1.00 24.15	6
ATOM	117	O	MET	261	-7.162	19.406	35.770	1.00 24.54	8
ATOM	118	N	ASP	262	-7.833	17.473	34.879	1.00 25.16	7
ATOM	119	CA	ASP	262	-9.110	17.508	35.598	1.00 25.45	6
ATOM	120	CB	ASP	262	-9.961	16.300	35.242	1.00 26.93	6
ATOM	121	CG	ASP	262	-11.339	16.360	35.889	1.00 29.88	6
ATOM	122	OD1	ASP	262	-11.610	15.590	36.883	1.00 28.67	8
ATOM	123	OD2	ASP	262	-12.221	17.185	35.441	1.00 30.00	8
ATOM	124	C	ASP	262	-8.854	17.514	37.109	1.00 26.43	6
ATOM	125	O	ASP	262	-9.537	18.201	37.881	1.00 24.36	8
ATOM	126	N	SER	263	-7.863	16.747	37.510	1.00 25.37	7
ATOM	127	CA	SER	263	-7.504	16.640	38.925	1.00 26.08	6
ATOM	128	CB	SER	263	-6.680	15.381	39.178	1.00 26.03	6
ATOM	129	OG	SER	263	-6.330	15.310	40.554	1.00 29.76	8
ATOM	130	C	SER	263	-6.688	17.860	39.380	1.00 26.66	6
ATOM	131	O	SER	263	-6.884	18.389	40.479	1.00 27.29	8
ATOM	132	N	TYR	264	-5.781	18.298	38.526	1.00 25.66	7
ATOM	133	CA	TYR	264	-4.883	19.427	38.845	1.00 26.94	6
ATOM	134	CB	TYR	264	-3.816	19.584	37.750	1.00 23.84	6
ATOM	135	CG	TYR	264	-2.605	20.414	38.199	1.00 26.14	6
ATOM	136	CD1	TYR	264	-2.442	21.726	37.735	1.00 25.63	6
ATOM	137	CE1	TYR	264	-1.338	22.485	38.145	1.00 26.64	6
ATOM	138	CD2	TYR	264	-1.655	19.863	39.071	1.00 26.12	6
ATOM	139	CE2	TYR	264	-0.552	20.623	39.482	1.00 25.98	6
ATOM	140	CZ	TYR	264	-0.394	21.935	39.020	1.00 28.14	6
ATOM	141	OH	TYR	264	0.675	22.675	39.421	1.00 28.24	8
ATOM	142	C	TYR	264	-5.642	20.781	38.976	1.00 30.53	6
ATOM	143	O	TYR	264	-5.343	21.598	39.861	1.00 30.88	8
ATOM	144	N	ASN	265	-6.615	20.992	38.093	1.00 32.53	7
ATOM	145	CA	ASN	265	-7.390	22.266	38.004	1.00 36.75	6
ATOM	146	CB	ASN	265	-8.413	22.173	36.882	1.00 35.41	6
ATOM	147	CG	ASN	265	-7.763	22.449	35.533	1.00 36.05	6
ATOM	148	OD1	ASN	265	-8.381	22.235	34.498	1.00 37.43	8
ATOM	149	ND2	ASN	265	-6.527	22.916	35.490	1.00 32.44	7
ATOM	150	C	ASN	265	-8.096	22.627	39.319	1.00 40.35	6
ATOM	151	O	ASN	265	-8.468	23.796	39.540	1.00 41.97	8
ATOM	152	N	LYS	266	-8.265	21.612	40.140	1.00 44.37	7
ATOM	153	CA	LYS	266	-8.838	21.756	41.487	1.00 48.45	6
ATOM	154	CB	LYS	266	-9.615	20.516	41.911	1.00 47.77	6
ATOM	155	CG	LYS	266	-10.433	19.902	40.803	1.00 48.86	6
ATOM	156	CD	LYS	266	-10.904	18.501	41.152	1.00 48.08	6

```
ATOM    157  CE  LYS   266     -11.996  18.008  40.218  1.00 48.29   6
ATOM    158  NZ  LYS   266     -12.623  16.770  40.684  1.00 48.28   7
ATOM    159  C   LYS   266      -7.712  21.866  42.490  1.00 51.12   6
ATOM    160  O   LYS   266      -7.208  20.862  42.998  1.00 52.51   8
ATOM    161  N   GLN   267      -7.307  23.078  42.788  1.00 53.97   7
ATOM    162  CA  GLN   267      -6.178  23.252  43.710  1.00 56.59   6
ATOM    163  CB  GLN   267      -4.953  22.820  43.018  1.00 56.46   6
ATOM    164  CG  GLN   267      -3.751  22.919  43.902  1.00 57.69   6
ATOM    165  CD  GLN   267      -2.535  22.395  43.195  1.00 57.98   6
ATOM    166  OE1 GLN   267      -2.418  21.189  43.015  1.00 57.87   8
ATOM    167  NE2 GLN   267      -1.626  23.238  42.766  1.00 57.72   7
ATOM    168  C   GLN   267      -6.084  24.690  44.192  1.00 58.17   6
ATOM    169  O   GLN   267      -6.472  25.624  43.466  1.00 59.03   8
ATOM    170  N   ARG   268      -5.445  24.867  45.372  1.00 60.05   7
ATOM    171  CA  ARG   268      -5.819  26.060  46.137  1.00 61.88   6
ATOM    172  CB  ARG   268      -6.737  25.574  47.256  1.00 62.04   6
ATOM    173  CG  ARG   268      -6.982  24.074  47.104  1.00 64.49   6
ATOM    174  CD  ARG   268      -7.363  23.262  48.349  1.00 67.10   6
ATOM    175  NE  ARG   268      -8.601  22.510  48.096  1.00 70.55   7
ATOM    176  CZ  ARG   268      -8.892  21.244  48.456  1.00 72.10   6
ATOM    177  NH1 ARG   268      -8.030  20.483  49.137  1.00 72.70   7
ATOM    178  NH2 ARG   268     -10.068  20.653  48.165  1.00 72.00   7
ATOM    179  C   ARG   268      -5.016  26.917  47.094  1.00 62.81   6
ATOM    180  O   ARG   268      -4.597  26.574  48.172  1.00 64.18   8
ATOM    181  N   MET   269      -4.869  28.184  46.907  1.00 63.86   7
ATOM    182  CA  MET   269      -4.433  28.750  48.138  1.00 64.43   6
ATOM    183  CB  MET   269      -2.982  29.206  48.225  1.00 64.17   6
ATOM    184  CG  MET   269      -2.536  29.212  49.727  1.00 65.70   6
ATOM    185  SD  MET   269      -1.401  27.918  50.212  1.00 66.13  16
ATOM    186  CE  MET   269      -1.903  27.117  51.731  1.00 67.05   6
ATOM    187  C   MET   269      -5.386  29.831  48.685  1.00 64.67   6
ATOM    188  O   MET   269      -5.630  28.771  49.823  1.00 65.69   8
ATOM    189  N   PRO   270      -5.851  30.858  49.550  1.00 64.77   7
ATOM    190  CD  PRO   270      -6.430  30.187  50.202  1.00 64.53   6
ATOM    191  CA  PRO   270      -6.434  32.160  50.320  1.00 64.23   6
ATOM    192  CB  PRO   270      -7.540  31.838  51.010  1.00 64.34   6
ATOM    193  CG  PRO   270      -7.592  30.375  51.244  1.00 64.44   6
ATOM    194  C   PRO   270      -6.398  33.640  49.829  1.00 64.19   6
ATOM    195  O   PRO   270      -6.136  34.046  49.116  1.00 65.06   8
ATOM    196  OXT PRO   270      -6.539  34.261  48.697  1.00 63.72   8
TER
ATOM      1  CB  ASP   286       0.382  33.769  65.422  1.00 54.24   6
ATOM      2  CG  ASP   286      -0.926  34.440  65.715  1.00 57.55   6
ATOM      3  OD1 ASP   286      -1.248  35.480  65.070  1.00 59.45   8
ATOM      4  OD2 ASP   286      -1.632  33.905  66.602  1.00 60.19   8
ATOM      5  C   ASP   286       0.955  31.742  64.116  1.00 49.99   6
ATOM      6  O   ASP   286       0.319  31.366  63.141  1.00 49.47   8
ATOM      7  N   ASP   286       0.793  31.628  66.627  1.00 50.96   7
ATOM      8  CA  ASP   286       0.252  32.246  65.375  1.00 51.66   6
ATOM      9  N   GLU   287       2.441  32.325  64.308  1.00 47.84   7
ATOM     10  CA  GLU   287       3.421  32.140  63.248  1.00 44.91   6
ATOM     11  CB  GLU   287       4.797  32.529  63.756  1.00 47.08   6
ATOM     12  CG  GLU   287       5.736  32.977  62.680  1.00 50.43   6
ATOM     13  CD  GLU   287       5.260  34.269  62.097  1.00 52.24   6
ATOM     14  OE1 GLU   287       5.593  35.362  62.617  1.00 56.48   8
ATOM     15  OE2 GLU   287       4.493  34.201  61.143  1.00 54.23   8
ATOM     16  C   GLU   287       3.482  30.659  62.840  1.00 41.62   6
ATOM     17  O   GLU   287       3.228  30.317  61.690  1.00 39.59   8
```

ATOM	18	N	PHE	288	3.899	29.811	63.793	1.00 37.52	7
ATOM	19	CA	PHE	288	3.973	28.367	63.577	1.00 34.85	6
ATOM	20	CB	PHE	288	4.285	27.639	64.875	1.00 32.00	6
ATOM	21	CG	PHE	288	4.337	26.175	64.724	1.00 30.44	6
ATOM	22	CD1	PHE	288	5.434	25.599	64.140	1.00 28.62	6
ATOM	23	CD2	PHE	288	3.330	25.366	65.262	1.00 30.62	6
ATOM	24	CE1	PHE	288	5.577	24.224	64.090	1.00 30.42	6
ATOM	25	CE2	PHE	288	3.451	23.975	65.227	1.00 31.08	6
ATOM	26	CZ	PHE	288	4.593	23.397	64.635	1.00 30.53	6
ATOM	27	C	PHE	288	2.617	27.856	63.067	1.00 33.95	6
ATOM	28	O	PHE	288	2.549	26.952	62.239	1.00 32.05	8
ATOM	29	N	LEU	289	1.582	27.911	63.398	1.00 32.30	7
ATOM	30	CA	LEU	289	0.168	27.754	63.062	1.00 31.78	6
ATOM	31	CB	LEU	289	-0.654	28.626	64.023	1.00 33.66	6
ATOM	32	CG	LEU	289	-1.875	28.012	64.721	1.00 35.60	6
ATOM	33	CD1	LEU	289	-1.703	26.450	64.928	1.00 37.21	6
ATOM	34	CD2	LEU	289	-2.049	28.729	66.088	1.00 35.17	6
ATOM	35	C	LEU	289	-0.068	28.152	61.568	1.00 30.12	6
ATOM	36	O	LEU	289	-0.854	27.506	60.826	1.00 28.60	8
ATOM	37	N	ILE	290	0.384	29.641	61.314	1.00 26.28	7
ATOM	38	CA	ILE	290	0.216	30.126	59.937	1.00 27.25	6
ATOM	39	CB	ILE	290	0.806	31.570	59.729	1.00 28.35	6
ATOM	40	CG2	ILE	290	0.723	31.925	58.292	1.00 29.13	6
ATOM	41	CG1	ILE	290	0.020	32.604	60.520	1.00 30.90	6
ATOM	42	CD1	ILE	290	-1.458	32.512	60.232	1.00 32.59	6
ATOM	43	C	ILE	290	0.965	29.177	58.947	1.00 23.80	6
ATOM	44	O	ILE	290	0.414	28.781	57.911	1.00 24.53	8
ATOM	45	N	LEU	291	2.235	28.907	59.252	1.00 21.55	7
ATOM	46	CA	LEU	291	3.088	27.981	58.477	1.00 20.53	6
ATOM	47	CB	LEU	291	4.454	27.861	59.169	1.00 18.08	6
ATOM	48	CG	LEU	291	5.352	29.105	59.000	1.00 19.61	6
ATOM	49	CD1	LEU	291	6.607	28.918	59.913	1.00 20.86	6
ATOM	50	CD2	LEU	291	5.784	29.237	57.523	1.00 19.68	6
ATOM	51	C	LEU	291	2.424	26.590	58.419	1.00 19.60	6
ATOM	52	O	LEU	291	2.383	25.913	57.360	1.00 18.98	8
ATOM	53	N	THR	292	1.918	26.130	59.566	1.00 19.80	7
ATOM	54	CA	THR	292	1.254	24.812	59.623	1.00 20.09	6
ATOM	55	CB	THR	292	0.745	24.467	61.067	1.00 20.79	6
ATOM	56	OG1	THR	292	1.875	24.221	61.917	1.00 21.38	8
ATOM	57	CG2	THR	292	-0.163	23.189	61.034	1.00 20.16	6
ATOM	58	C	THR	292	0.044	24.718	58.688	1.00 21.47	6
ATOM	59	O	THR	292	-0.172	23.712	58.004	1.00 19.53	8
ATOM	60	N	GLU	293	-0.727	25.802	58.638	1.00 21.67	7
ATOM	61	CA	GLU	293	-1.906	25.811	57.802	1.00 22.91	6
ATOM	62	CB	GLU	293	-2.698	27.072	58.070	1.00 25.01	6
ATOM	63	CG	GLU	293	-4.092	27.071	57.454	1.00 31.18	6
ATOM	64	CD	GLU	293	-4.991	28.192	58.069	1.00 34.78	6
ATOM	65	OE1	GLU	293	-6.069	28.490	57.493	1.00 36.56	8
ATOM	66	OE2	GLU	293	-4.619	28.767	59.127	1.00 35.69	8
ATOM	67	C	GLU	293	-1.480	25.738	56.352	1.00 21.17	6
ATOM	68	O	GLU	293	-2.092	25.036	55.556	1.00 18.47	8
ATOM	69	N	MET	294	-0.445	26.504	56.001	1.00 20.96	7
ATOM	70	CA	MET	294	0.049	26.446	54.632	1.00 21.46	6
ATOM	71	CB	MET	294	1.173	27.437	54.413	1.00 22.39	6
ATOM	72	CG	MET	294	0.776	28.861	54.668	1.00 25.97	6
ATOM	73	SD	MET	294	2.260	29.945	54.657	1.00 27.73	16
ATOM	74	CE	MET	294	1.488	31.565	54.140	1.00 30.04	6
ATOM	75	C	MET	294	0.557	25.031	54.258	1.00 19.87	6

ATOM	76	O	MET	294	0.224	24.534	53.199	1.00	19.58	8
ATOM	77	N	ALA	295	1.380	24.415	55.111	1.00	18.94	7
ATOM	78	CA	ALA	295	1.884	23.064	54.816	1.00	19.37	6
ATOM	79	CB	ALA	295	2.788	22.619	55.888	1.00	18.19	6
ATOM	80	C	ALA	295	0.729	22.082	54.696	1.00	17.66	6
ATOM	81	O	ALA	295	0.723	21.214	53.839	1.00	16.19	8
ATOM	82	N	THR	296	-0.267	22.229	55.576	1.00	18.37	7
ATOM	83	CA	THR	296	-1.419	21.336	55.580	1.00	18.66	6
ATOM	84	CB	THR	296	-2.353	21.684	56.754	1.00	18.29	6
ATOM	85	OG1	THR	296	-1.714	21.302	57.976	1.00	20.03	8
ATOM	86	CG2	THR	296	-3.659	21.011	56.629	1.00	20.09	6
ATOM	87	C	THR	296	-2.147	21.420	54.256	1.00	17.86	6
ATOM	88	O	THR	296	-2.531	20.391	53.664	1.00	18.69	8
ATOM	89	N	ASN	297	-2.332	22.638	53.780	1.00	18.24	7
ATOM	90	CA	ASN	297	-2.957	22.844	52.480	1.00	19.98	6
ATOM	91	CB	ASN	297	-2.966	24.320	52.125	1.00	20.69	6
ATOM	92	CG	ASN	297	-3.544	24.558	50.764	1.00	27.62	6
ATOM	93	OD1	ASN	297	-2.839	24.927	49.805	1.00	29.49	8
ATOM	94	ND2	ASN	297	-4.862	24.303	50.631	1.00	31.14	7
ATOM	95	C	ASN	297	-2.123	22.081	51.404	1.00	17.67	6
ATOM	96	O	ASN	297	-2.677	21.386	50.552	1.00	14.27	8
ATOM	97	N	HIS	298	-0.794	22.229	51.463	1.00	17.59	7
ATOM	98	CA	HIS	298	0.054	21.550	50.483	1.00	18.04	6
ATOM	99	CB	HIS	298	1.512	21.952	50.615	1.00	21.15	6
ATOM	100	CG	HIS	298	1.840	23.236	49.922	1.00	22.19	6
ATOM	101	CD2	HIS	298	2.341	24.404	50.396	1.00	23.65	6
ATOM	102	ND1	HIS	298	1.729	23.392	48.554	1.00	22.66	7
ATOM	103	CE1	HIS	298	2.162	24.593	48.215	1.00	23.47	6
ATOM	104	NE2	HIS	298	2.541	25.231	49.310	1.00	21.08	7
ATOM	105	C	HIS	298	-0.045	20.063	50.531	1.00	18.06	6
ATOM	106	O	HIS	298	-0.116	19.423	49.465	1.00	20.51	8
ATOM	107	N	VAL	299	-0.043	19.491	51.716	1.00	18.80	7
ATOM	108	CA	VAL	299	-0.116	18.044	51.856	1.00	18.34	6
ATOM	109	CB	VAL	299	0.097	17.623	53.299	1.00	19.15	6
ATOM	110	CG1	VAL	299	-0.044	16.109	53.454	1.00	19.87	6
ATOM	111	CG2	VAL	299	1.461	18.029	53.717	1.00	24.63	6
ATOM	112	C	VAL	299	-1.480	17.552	51.403	1.00	18.54	6
ATOM	113	O	VAL	299	-1.566	16.556	50.741	1.00	15.62	8
ATOM	114	N	GLN	300	-2.567	18.260	51.740	1.00	17.99	7
ATOM	115	CA	GLN	300	-3.893	17.782	51.294	1.00	19.01	6
ATOM	116	CB	GLN	300	-4.965	18.704	51.846	1.00	22.22	6
ATOM	117	CG	GLN	300	-4.915	18.952	53.352	1.00	30.87	6
ATOM	118	CD	GLN	300	-5.717	17.959	54.103	1.00	34.36	6
ATOM	119	OE1	GLN	300	-5.795	16.804	53.706	1.00	39.66	8
ATOM	120	NE2	GLN	300	-6.305	18.381	55.213	1.00	37.60	7
ATOM	121	C	GLN	300	-4.008	17.760	49.732	1.00	18.19	6
ATOM	122	O	GLN	300	-4.536	16.819	49.136	1.00	16.90	8
ATOM	123	N	VAL	301	-3.562	18.821	49.070	1.00	18.12	7
ATOM	124	CA	VAL	301	-3.638	18.831	47.622	1.00	19.51	6
ATOM	125	CB	VAL	301	-3.294	20.227	47.021	1.00	22.21	6
ATOM	126	CG1	VAL	301	-4.198	21.283	47.562	1.00	23.03	6
ATOM	127	CG2	VAL	301	-1.897	20.566	47.304	1.00	24.65	6
ATOM	128	C	VAL	301	-2.663	17.757	47.039	1.00	18.49	6
ATOM	129	O	VAL	301	-2.937	17.159	46.019	1.00	18.00	8
ATOM	130	N	LEU	302	-1.512	17.536	47.680	1.00	17.88	7
ATOM	131	CA	LEU	302	-0.612	16.471	47.208	1.00	17.22	6
ATOM	132	CB	LEU	302	0.602	16.373	48.124	1.00	17.43	6
ATOM	133	CG	LEU	302	1.573	15.178	47.873	1.00	19.18	6

ATOM	134	CD1	LEU	302	2.236	15.266	46.455	1.00 18.97	6
ATOM	135	CD2	LEU	302	2.669	15.147	49.046	1.00 16.64	6
ATOM	136	C	LEU	302	-1.364	15.085	47.248	1.00 18.20	6
ATOM	137	O	LEU	302	-1.399	14.300	46.289	1.00 16.31	8
ATOM	138	N	VAL	303	-1.888	14.763	48.416	1.00 18.28	7
ATOM	139	CA	VAL	303	-2.612	13.499	48.541	1.00 17.18	6
ATOM	140	CB	VAL	303	-3.250	13.369	49.962	1.00 16.21	6
ATOM	141	CG1	VAL	303	-4.308	12.217	49.974	1.00 17.81	6
ATOM	142	CG2	VAL	303	-2.131	13.205	51.020	1.00 18.44	6
ATOM	143	C	VAL	303	-3.725	13.440	47.499	1.00 17.48	6
ATOM	144	O	VAL	303	-3.887	12.402	46.839	1.00 17.05	8
ATOM	145	N	GLU	304	-4.509	14.511	47.322	1.00 17.74	7
ATOM	146	CA	GLU	304	-5.622	14.425	46.364	1.00 20.30	6
ATOM	147	CB	GLU	304	-6.591	15.623	46.510	1.00 23.98	6
ATOM	148	CG	GLU	304	-7.226	15.679	47.913	1.00 28.15	6
ATOM	149	CD	GLU	304	-7.981	14.371	48.235	1.00 29.95	6
ATOM	150	OE1	GLU	304	-8.899	14.034	47.482	1.00 31.97	8
ATOM	151	OE2	GLU	304	-7.652	13.667	49.189	1.00 29.89	8
ATOM	152	C	GLU	304	-5.190	14.255	44.889	1.00 20.90	6
ATOM	153	O	GLU	304	-5.820	13.527	44.082	1.00 21.49	8
ATOM	154	N	PHE	305	-4.108	14.910	44.544	1.00 19.35	7
ATOM	155	CA	PHE	305	-3.651	14.820	43.183	1.00 17.57	6
ATOM	156	CB	PHE	305	-2.576	15.908	42.939	1.00 17.86	6
ATOM	157	CG	PHE	305	-2.039	15.948	41.524	1.00 18.48	6
ATOM	158	CD1	PHE	305	-2.891	16.115	40.466	1.00 18.87	6
ATOM	159	CD2	PHE	305	-0.672	15.850	41.285	1.00 22.41	6
ATOM	160	CE1	PHE	305	-2.419	16.186	39.120	1.00 20.69	6
ATOM	161	CE2	PHE	305	-0.138	15.921	39.958	1.00 23.10	6
ATOM	162	CZ	PHE	305	-1.026	16.091	38.848	1.00 22.51	6
ATOM	163	C	PHE	305	-3.059	13.436	42.989	1.00 16.51	6
ATOM	164	O	PHE	305	-3.325	12.755	41.979	1.00 15.12	8
ATOM	165	N	THR	306	-2.230	13.032	43.933	1.00 15.89	7
ATOM	166	CA	THR	306	-1.542	11.705	43.868	1.00 16.43	6
ATOM	167	CB	THR	306	-0.650	11.473	45.165	1.00 15.13	6
ATOM	168	OG1	THR	306	0.367	12.498	45.246	1.00 14.50	8
ATOM	169	CG2	THR	306	0.028	10.103	45.143	1.00 16.67	6
ATOM	170	C	THR	306	-2.495	10.526	43.667	1.00 15.78	6
ATOM	171	O	THR	306	-2.260	9.689	42.810	1.00 15.88	8
ATOM	172	N	LYS	307	-3.596	10.486	44.420	1.00 16.48	7
ATOM	173	CA	LYS	307	-4.516	9.371	44.300	1.00 18.55	6
ATOM	174	CB	LYS	307	-5.601	9.465	45.401	1.00 17.71	6
ATOM	175	CG	LYS	307	-6.581	10.619	45.227	1.00 20.71	6
ATOM	176	CD	LYS	307	-7.339	10.932	46.549	1.00 24.94	6
ATOM	177	CE	LYS	307	-8.366	9.878	46.684	1.00 25.72	6
ATOM	178	NZ	LYS	307	-9.072	9.871	48.045	1.00 29.69	7
ATOM	179	C	LYS	307	-5.157	9.282	42.905	1.00 18.63	6
ATOM	180	O	LYS	307	-5.564	8.221	42.502	1.00 21.33	8
ATOM	181	N	LYS	308	-5.253	10.391	42.189	1.00 19.50	7
ATOM	182	CA	LYS	308	-5.840	10.368	40.849	1.00 19.00	6
ATOM	183	CB	LYS	308	-6.540	11.687	40.556	1.00 21.16	6
ATOM	184	CG	LYS	308	-7.631	12.080	41.516	1.00 25.16	6
ATOM	185	CD	LYS	308	-8.732	11.053	41.574	1.00 27.43	6
ATOM	186	CE	LYS	308	-9.740	11.549	42.583	1.00 31.55	6
ATOM	187	NZ	LYS	308	-10.864	10.642	42.907	1.00 33.60	7
ATOM	188	C	LYS	308	-4.796	10.142	39.739	1.00 20.57	6
ATOM	189	O	LYS	308	-5.170	10.129	38.545	1.00 17.08	8
ATOM	190	N	LEU	309	-3.501	10.005	40.077	1.00 19.34	7
ATOM	191	CA	LEU	309	-2.536	9.764	38.992	1.00 20.62	6

```
ATOM    192  CB  LEU  309      -1.094   9.683  39.489  1.00 19.62    6
ATOM    193  CG  LEU  309      -0.388  11.010  39.844  1.00 21.00    6
ATOM    194  CD1 LEU  309      -1.298  11.787  40.514  1.00 23.97    6
ATOM    195  CD2 LEU  309       0.803  10.828  40.790  1.00 19.53    6
ATOM    196  C   LEU  309      -2.828   8.475  38.224  1.00 20.21    6
ATOM    197  O   LEU  309      -3.076   7.409  38.815  1.00 18.44    8
ATOM    198  N   PRO  310      -2.703   8.527  36.889  1.00 22.57    7
ATOM    199  CD  PRO  310      -2.291   9.642  36.014  1.00 23.56    6
ATOM    200  CA  PRO  310      -2.984   7.323  36.091  1.00 22.89    6
ATOM    201  CB  PRO  310      -2.776   7.798  34.624  1.00 24.04    6
ATOM    202  CG  PRO  310      -1.821   8.912  34.783  1.00 25.27    6
ATOM    203  C   PRO  310      -2.096   6.158  36.485  1.00 22.58    6
ATOM    204  O   PRO  310      -0.879   6.270  36.476  1.00 21.83    8
ATOM    205  N   GLY  311      -2.727   5.037  36.832  1.00 20.55    7
ATOM    206  CA  GLY  311      -1.963   3.861  37.265  1.00 21.62    6
ATOM    207  C   GLY  311      -1.642   3.820  38.757  1.00 18.98    6
ATOM    208  O   GLY  311      -1.220   2.785  39.279  1.00 18.35    8
ATOM    209  N   PHE  312      -1.843   4.928  39.479  1.00 21.41    7
ATOM    210  CA  PHE  312      -1.450   4.920  40.903  1.00 19.93    6
ATOM    211  CB  PHE  312      -1.679   6.307  41.544  1.00 20.01    6
ATOM    212  CG  PHE  312      -0.906   6.496  42.794  1.00 16.33    6
ATOM    213  CD1 PHE  312       0.430   6.875  42.757  1.00 18.90    6
ATOM    214  CD2 PHE  312      -1.507   6.270  44.029  1.00 20.84    6
ATOM    215  CE1 PHE  312       1.172   7.039  43.958  1.00 17.69    6
ATOM    216  CE2 PHE  312      -0.788   6.425  45.235  1.00 19.69    6
ATOM    217  CZ  PHE  312       0.560   6.817  45.182  1.00 18.11    6
ATOM    218  C   PHE  312      -2.160   3.841  41.716  1.00 21.58    6
ATOM    219  O   PHE  312      -1.590   3.237  42.622  1.00 19.65    8
ATOM    220  N   GLN  313      -3.348   3.539  41.367  1.00 23.23    7
ATOM    221  CA  GLN  313      -4.014   2.563  42.216  1.00 25.13    6
ATOM    222  CB  GLN  313      -5.525   2.588  41.921  1.00 26.97    6
ATOM    223  CG  GLN  313      -6.130   3.954  42.336  1.00 31.32    6
ATOM    224  CD  GLN  313      -5.793   4.264  43.792  1.00 32.76    6
ATOM    225  OE1 GLN  313      -4.948   5.140  44.136  1.00 25.45    8
ATOM    226  NE2 GLN  313      -6.483   3.512  44.680  1.00 36.75    7
ATOM    227  C   GLN  313      -3.421   1.153  42.092  1.00 26.40    6
ATOM    228  O   GLN  313      -3.775   0.256  42.850  1.00 28.47    8
ATOM    229  N   THR  314      -2.757   0.897  40.858  1.00 23.84    7
ATOM    230  CA  THR  314      -2.207  -0.476  40.645  1.00 24.52    6
ATOM    231  CB  THR  314      -1.833  -0.703  39.166  1.00 23.30    6
ATOM    232  OG1 THR  314      -0.623   0.007  38.874  1.00 22.33    8
ATOM    233  CG2 THR  314      -2.926  -0.175  38.258  1.00 24.71    6
ATOM    234  C   THR  314      -0.904  -0.784  41.458  1.00 23.15    6
ATOM    235  O   THR  314      -0.395  -1.928  41.451  1.00 23.42    8
ATOM    236  N   LEU  315      -0.335   0.221  42.125  1.00 19.70    7
ATOM    237  CA  LEU  315       0.916   0.005  42.855  1.00 18.48    6
ATOM    238  CB  LEU  315       1.645   1.361  43.069  1.00 17.29    6
ATOM    239  CG  LEU  315       2.054   2.194  41.830  1.00 17.40    6
ATOM    240  CD1 LEU  315       2.693   3.602  42.217  1.00 14.19    6
ATOM    241  CD2 LEU  315       3.069   1.301  40.990  1.00 17.25    6
ATOM    242  C   LEU  315       0.789  -0.643  44.223  1.00 18.72    6
ATOM    243  O   LEU  315      -0.185  -0.454  44.932  1.00 20.69    8
ATOM    244  N   ASP  316       1.826  -1.349  44.616  1.00 19.50    7
ATOM    245  CA  ASP  316       1.942  -1.967  45.935  1.00 19.20    6
ATOM    246  CB  ASP  316       3.379  -2.450  46.107  1.00 20.18    6
ATOM    247  CG  ASP  316       3.698  -2.794  47.540  1.00 25.37    6
ATOM    248  OD1 ASP  316       3.889  -1.872  48.362  1.00 19.03    8
ATOM    249  OD2 ASP  316       3.725  -4.001  47.870  1.00 25.96    8
```

ATOM	250	C	ASP	316	1.640	-0.813	46.969	1.00	21.35	6
ATOM	251	O	ASP	316	2.138	0.337	46.806	1.00	18.68	8
ATOM	252	N	HIS	317	0.877	-1.123	48.030	1.00	19.74	7
ATOM	253	CA	HIS	317	0.469	-0.114	49.046	1.00	23.76	6
ATOM	254	CB	HIS	317	-0.545	-0.735	50.037	1.00	26.00	6
ATOM	255	CG	HIS	317	-1.875	-1.090	49.421	1.00	30.33	6
ATOM	256	CD2	HIS	317	-2.992	-1.617	49.978	1.00	29.44	6
ATOM	257	ND1	HIS	317	-2.178	-0.884	48.086	1.00	32.91	7
ATOM	258	CE1	HIS	317	-3.425	-1.254	47.853	1.00	32.13	6
ATOM	259	NE2	HIS	317	-3.936	-1.704	48.986	1.00	34.72	7
ATOM	260	C	HIS	317	1.650	0.514	49.810	1.00	22.45	6
ATOM	261	O	HIS	317	1.704	1.735	50.073	1.00	22.34	8
ATOM	262	N	GLU	318	2.615	-0.277	50.210	1.00	20.95	7
ATOM	263	CA	GLU	318	3.731	0.392	50.844	1.00	21.24	6
ATOM	264	CB	GLU	318	4.707	-0.617	51.366	1.00	24.39	6
ATOM	265	CG	GLU	318	4.078	-1.508	52.430	1.00	32.15	6
ATOM	266	CD	GLU	318	4.981	-2.644	52.751	1.00	35.27	6
ATOM	267	OE1	GLU	318	6.173	-2.389	52.981	1.00	36.95	8
ATOM	268	OE2	GLU	318	4.515	-3.782	52.756	1.00	39.48	8
ATOM	269	C	GLU	318	4.465	1.349	49.875	1.00	21.26	6
ATOM	270	O	GLU	318	4.956	2.426	50.290	1.00	17.47	8
ATOM	271	N	ASP	319	4.577	0.950	48.599	1.00	19.59	7
ATOM	272	CA	ASP	319	5.313	1.796	47.654	1.00	18.68	6
ATOM	273	CB	ASP	319	5.565	1.118	46.289	1.00	18.49	6
ATOM	274	CG	ASP	319	6.682	0.052	46.331	1.00	24.88	6
ATOM	275	OD1	ASP	319	7.425	-0.054	47.360	1.00	23.92	8
ATOM	276	OD2	ASP	319	6.785	-0.672	45.300	1.00	24.68	8
ATOM	277	C	ASP	319	4.538	3.077	47.426	1.00	17.13	6
ATOM	278	O	ASP	319	5.173	4.173	47.293	1.00	15.40	8
ATOM	279	N	GLN	320	3.190	2.968	47.441	1.00	16.62	7
ATOM	280	CA	GLN	320	2.393	4.186	47.250	1.00	15.75	6
ATOM	281	CB	GLN	320	0.867	3.924	47.274	1.00	14.55	6
ATOM	282	CG	GLN	320	0.250	3.078	46.102	1.00	15.80	6
ATOM	283	CD	GLN	320	-1.251	2.754	46.374	1.00	18.55	6
ATOM	284	OE1	GLN	320	-1.639	2.464	47.530	1.00	21.01	8
ATOM	285	NE2	GLN	320	-2.073	2.798	45.353	1.00	15.19	7
ATOM	286	C	GLN	320	2.743	5.215	48.337	1.00	15.42	6
ATOM	287	O	GLN	320	2.917	6.407	48.047	1.00	15.10	8
ATOM	288	N	ILE	321	2.792	4.781	49.586	1.00	14.62	7
ATOM	289	CA	ILE	321	3.085	5.717	50.641	1.00	16.80	6
ATOM	290	CB	ILE	321	2.914	5.087	52.061	1.00	17.30	6
ATOM	291	CG2	ILE	321	3.411	6.037	53.174	1.00	17.43	6
ATOM	292	CG1	ILE	321	1.451	4.740	52.325	1.00	20.51	6
ATOM	293	CD1	ILE	321	0.480	5.863	52.214	1.00	20.43	6
ATOM	294	C	ILE	321	4.515	6.223	50.489	1.00	16.01	6
ATOM	295	O	ILE	321	4.795	7.390	50.749	1.00	17.42	8
ATOM	296	N	ALA	322	5.434	5.335	50.094	1.00	15.05	7
ATOM	297	CA	ALA	322	6.817	5.792	49.927	1.00	13.64	6
ATOM	298	CB	ALA	322	7.705	4.636	49.571	1.00	14.95	6
ATOM	299	C	ALA	322	6.956	6.889	48.837	1.00	14.45	6
ATOM	300	O	ALA	322	7.837	7.712	48.909	1.00	14.12	8
ATOM	301	N	LEU	323	6.129	6.838	47.798	1.00	13.09	7
ATOM	302	CA	LEU	323	6.185	7.820	46.736	1.00	12.90	6
ATOM	303	CB	LEU	323	5.335	7.364	45.554	1.00	13.56	6
ATOM	304	CG	LEU	323	5.872	6.173	44.746	1.00	13.89	6
ATOM	305	CD1	LEU	323	4.980	5.830	43.625	1.00	17.08	6
ATOM	306	CD2	LEU	323	7.296	6.616	44.144	1.00	16.42	6
ATOM	307	C	LEU	323	5.596	9.141	47.294	1.00	15.12	6

ATOM	308	O	LEU	323	6.105	10.200	47.031	1.00	12.70	8
ATOM	309	N	LEU	324	4.509	9.028	48.043	1.00	14.66	7
ATOM	310	CA	LEU	324	3.835	10.189	48.586	1.00	16.63	6
ATOM	311	CB	LEU	324	2.600	9.738	49.393	1.00	16.39	6
ATOM	312	CG	LEU	324	1.730	10.820	50.048	1.00	17.06	6
ATOM	313	CD1	LEU	324	0.796	11.523	48.959	1.00	14.93	6
ATOM	314	CD2	LEU	324	0.830	10.132	51.172	1.00	17.39	6
ATOM	315	C	LEU	324	4.769	10.966	49.483	1.00	16.68	6
ATOM	316	O	LEU	324	4.963	12.164	49.335	1.00	13.80	8
ATOM	317	N	LYS	325	5.355	10.268	50.439	1.00	16.50	7
ATOM	318	CA	LYS	325	6.249	10.950	51.356	1.00	17.35	6
ATOM	319	CB	LYS	325	6.574	10.007	52.549	1.00	18.02	6
ATOM	320	CG	LYS	325	5.337	9.621	53.416	1.00	19.36	6
ATOM	321	CD	LYS	325	5.733	8.612	54.460	1.00	22.22	6
ATOM	322	CE	LYS	325	4.597	8.289	55.400	1.00	26.08	6
ATOM	323	NZ	LYS	325	5.009	7.369	56.518	1.00	27.52	7
ATOM	324	C	LYS	325	7.579	11.456	50.669	1.00	18.31	6
ATOM	325	O	LYS	325	8.069	12.528	50.979	1.00	17.70	8
ATOM	326	N	GLY	326	8.142	10.599	49.805	1.00	17.79	7
ATOM	327	CA	GLY	326	9.354	10.910	49.086	1.00	16.62	6
ATOM	328	C	GLY	326	9.145	12.181	48.210	1.00	16.82	6
ATOM	329	O	GLY	326	10.115	12.892	47.944	1.00	15.87	8
ATOM	330	N	SER	327	7.904	12.479	47.802	1.00	13.98	7
ATOM	331	CA	SER	327	7.668	13.640	46.919	1.00	13.96	6
ATOM	332	CB	SER	327	6.663	13.252	45.806	1.00	15.72	6
ATOM	333	OG	SER	327	5.352	13.032	46.367	1.00	17.33	8
ATOM	334	C	SER	327	7.136	14.943	47.589	1.00	14.59	6
ATOM	335	O	SER	327	7.060	15.968	46.914	1.00	12.64	8
ATOM	336	N	ALA	328	6.703	14.860	48.858	1.00	14.21	7
ATOM	337	CA	ALA	328	6.067	15.995	49.559	1.00	16.31	6
ATOM	338	CB	ALA	328	5.710	15.643	51.028	1.00	14.45	6
ATOM	339	C	ALA	328	6.755	17.348	49.512	1.00	15.67	6
ATOM	340	O	ALA	328	6.104	18.291	49.129	1.00	16.81	8
ATOM	341	N	VAL	329	8.056	17.419	49.818	1.00	15.11	7
ATOM	342	CA	VAL	329	8.797	18.669	49.801	1.00	14.39	6
ATOM	343	CB	VAL	329	10.193	18.472	50.471	1.00	15.93	6
ATOM	344	CG1	VAL	329	10.996	19.721	50.324	1.00	14.45	6
ATOM	345	CG2	VAL	329	10.006	17.992	51.946	1.00	18.03	6
ATOM	346	C	VAL	329	8.955	19.166	48.378	1.00	15.82	6
ATOM	347	O	VAL	329	8.639	20.309	48.107	1.00	15.63	8
ATOM	348	N	GLU	330	9.390	18.308	47.441	1.00	14.35	7
ATOM	349	CA	GLU	330	9.523	18.808	46.081	1.00	16.61	6
ATOM	350	CB	GLU	330	10.155	17.784	45.127	1.00	17.85	6
ATOM	351	CG	GLU	330	11.579	17.359	45.457	1.00	19.53	6
ATOM	352	CD	GLU	330	11.904	15.959	44.863	1.00	22.28	6
ATOM	353	OE1	GLU	330	11.344	15.676	43.785	1.00	16.30	8
ATOM	354	OE2	GLU	330	12.729	15.180	45.437	1.00	18.52	8
ATOM	355	C	GLU	330	8.188	19.282	45.482	1.00	16.03	6
ATOM	356	O	GLU	330	8.184	20.319	44.811	1.00	16.48	8
ATOM	357	N	ALA	331	7.097	18.572	45.719	1.00	15.19	7
ATOM	358	CA	ALA	331	5.781	18.982	45.169	1.00	16.21	6
ATOM	359	CB	ALA	331	4.698	17.954	45.510	1.00	18.20	6
ATOM	360	C	ALA	331	5.371	20.312	45.749	1.00	14.82	6
ATOM	361	O	ALA	331	4.797	21.166	45.056	1.00	14.73	8
ATOM	362	N	MET	332	5.647	20.482	47.019	1.00	14.40	7
ATOM	363	CA	MET	332	5.303	21.728	47.667	1.00	16.90	6
ATOM	364	CB	MET	332	5.581	21.650	49.171	1.00	16.44	6
ATOM	365	CG	MET	332	5.472	22.995	49.820	1.00	17.98	6

ATOM	366	SD	MET	332	5.578	22.728	51.691	1.00	25.41	16
ATOM	367	CE	MET	332	7.346	22.648	51.873	1.00	20.17	6
ATOM	368	C	MET	332	6.067	22.929	47.045	1.00	16.28	6
ATOM	369	O	MET	332	5.489	24.017	46.846	1.00	14.37	8
ATOM	370	N	PHE	333	7.363	22.737	46.759	1.00	16.46	7
ATOM	371	CA	PHE	333	8.120	23.802	46.113	1.00	16.88	6
ATOM	372	CB	PHE	333	9.651	23.556	46.190	1.00	15.57	6
ATOM	373	CG	PHE	333	10.225	24.020	47.513	1.00	16.37	6
ATOM	374	CD1	PHE	333	10.633	25.365	47.684	1.00	19.32	6
ATOM	375	CD2	PHE	333	10.160	23.188	48.634	1.00	16.95	6
ATOM	376	CE1	PHE	333	10.946	25.890	49.008	1.00	20.18	6
ATOM	377	CE2	PHE	333	10.472	23.690	49.957	1.00	19.20	6
ATOM	378	CZ	PHE	333	10.853	25.043	50.131	1.00	18.12	6
ATOM	379	C	PHE	333	7.695	24.044	44.683	1.00	18.09	6
ATOM	380	O	PHE	333	7.646	25.172	44.251	1.00	18.76	8
ATOM	381	N	LEU	334	7.409	22.989	43.937	1.00	17.85	7
ATOM	382	CA	LEU	334	6.958	23.153	42.584	1.00	18.30	6
ATOM	383	CB	LEU	334	6.809	21.764	42.025	1.00	18.77	6
ATOM	384	CG	LEU	334	7.155	21.507	40.592	1.00	26.18	6
ATOM	385	CD1	LEU	334	6.960	19.943	40.217	1.00	24.92	6
ATOM	386	CD2	LEU	334	6.331	22.317	39.812	1.00	28.42	6
ATOM	387	C	LEU	334	5.598	23.904	42.579	1.00	17.11	6
ATOM	388	O	LEU	334	5.357	24.832	41.793	1.00	15.65	8
ATOM	389	N	ARG	335	4.690	23.482	43.439	1.00	16.49	7
ATOM	390	CA	ARG	335	3.399	24.176	43.524	1.00	18.43	6
ATOM	391	CB	ARG	335	2.484	23.454	44.460	1.00	17.09	6
ATOM	392	CG	ARG	335	1.156	24.182	44.525	1.00	21.57	6
ATOM	393	CD	ARG	335	0.176	23.373	45.352	1.00	21.97	6
ATOM	394	NE	ARG	335	-1.089	24.081	45.471	1.00	27.76	7
ATOM	395	CZ	ARG	335	-1.783	24.172	46.606	1.00	28.73	6
ATOM	396	NH1	ARG	335	-1.319	23.581	47.717	1.00	31.14	7
ATOM	397	NH2	ARG	335	-2.894	24.888	46.653	1.00	29.24	7
ATOM	398	C	ARG	335	3.494	25.687	43.962	1.00	19.12	6
ATOM	399	O	ARG	335	2.788	26.537	43.441	1.00	16.26	8
ATOM	400	N	SER	336	4.312	25.980	44.978	1.00	18.56	7
ATOM	401	CA	SER	336	4.544	27.347	45.432	1.00	18.60	6
ATOM	402	CB	SER	336	5.559	27.322	46.590	1.00	18.30	6
ATOM	403	OG	SER	336	5.002	26.665	47.691	1.00	29.88	8
ATOM	404	C	SER	336	5.188	28.112	44.234	1.00	18.04	6
ATOM	405	O	SER	336	4.893	29.303	43.988	1.00	18.32	8
ATOM	406	N	ALA	337	6.033	27.419	43.467	1.00	16.79	7
ATOM	407	CA	ALA	337	6.676	28.097	42.346	1.00	17.46	6
ATOM	408	CB	ALA	337	7.796	27.201	41.665	1.00	18.26	6
ATOM	409	C	ALA	337	5.643	28.541	41.331	1.00	18.29	6
ATOM	410	O	ALA	337	5.713	29.677	40.829	1.00	17.95	8
ATOM	411	N	GLU	338	4.674	27.670	41.042	1.00	19.09	7
ATOM	412	CA	GLU	338	3.637	28.006	40.090	1.00	21.75	6
ATOM	413	CB	GLU	338	2.759	26.775	39.807	1.00	22.98	6
ATOM	414	CG	GLU	338	1.577	27.106	38.908	1.00	27.45	6
ATOM	415	CD	GLU	338	0.641	25.937	38.689	1.00	30.18	6
ATOM	416	OE1	GLU	338	0.424	25.154	39.626	1.00	34.22	8
ATOM	417	OE2	GLU	338	0.081	25.793	37.564	1.00	34.98	8
ATOM	418	C	GLU	338	2.782	29.173	40.622	1.00	21.21	6
ATOM	419	O	GLU	338	2.464	30.127	39.887	1.00	21.40	8
ATOM	420	N	ILE	339	2.432	29.119	41.898	1.00	21.45	7
ATOM	421	CA	ILE	339	1.636	30.185	42.482	1.00	21.47	6
ATOM	422	CB	ILE	339	1.255	29.863	43.943	1.00	19.46	6
ATOM	423	CG2	ILE	339	0.560	31.059	44.597	1.00	18.31	6

ATOM	424	CG1	ILE	339	0.321	28.655	43.994	1.00	21.28	6
ATOM	425	CD1	ILE	339	0.215	28.014	45.481	1.00	21.24	6
ATOM	426	C	ILE	339	2.356	31.542	42.432	1.00	22.43	6
ATOM	427	O	ILE	339	1.744	32.541	42.102	1.00	22.81	8
ATOM	428	N	PHE	340	3.631	31.579	42.779	1.00	23.06	7
ATOM	429	CA	PHE	340	4.365	32.829	42.746	1.00	24.91	6
ATOM	430	CB	PHE	340	5.753	32.634	43.320	1.00	27.89	6
ATOM	431	CG	PHE	340	5.837	32.969	44.752	1.00	33.81	6
ATOM	432	CD1	PHE	340	5.162	32.200	45.713	1.00	34.20	6
ATOM	433	CD2	PHE	340	6.534	34.126	45.155	1.00	36.42	6
ATOM	434	CE1	PHE	340	5.177	32.590	47.082	1.00	37.61	6
ATOM	435	CE2	PHE	340	6.560	34.532	46.511	1.00	38.51	6
ATOM	436	CZ	PHE	340	5.876	33.766	47.479	1.00	37.64	6
ATOM	437	C	PHE	340	4.498	33.429	41.364	1.00	24.41	6
ATOM	438	O	PHE	340	4.479	34.639	41.225	1.00	23.54	8
ATOM	439	N	ASN	341	4.665	32.577	40.352	1.00	23.80	7
ATOM	440	CA	ASN	341	4.820	33.038	38.983	1.00	24.65	6
ATOM	441	CB	ASN	341	5.600	32.001	38.121	1.00	23.93	6
ATOM	442	CG	ASN	341	7.109	32.073	38.315	1.00	22.97	6
ATOM	443	OD1	ASN	341	7.755	32.970	37.793	1.00	23.91	8
ATOM	444	ND2	ASN	341	7.670	31.126	39.048	1.00	20.60	7
ATOM	445	C	ASN	341	3.495	33.321	38.256	1.00	25.81	6
ATOM	446	O	ASN	341	3.414	34.302	37.509	1.00	27.47	8
ATOM	447	N	LYS	342	2.496	32.466	38.439	1.00	24.48	7
ATOM	448	CA	LYS	342	1.247	32.608	37.700	1.00	25.08	6
ATOM	449	CB	LYS	342	0.876	31.259	37.085	1.00	22.98	6
ATOM	450	CG	LYS	342	2.062	30.531	36.494	1.00	24.27	6
ATOM	451	CD	LYS	342	1.647	29.193	35.945	1.00	28.99	6
ATOM	452	CE	LYS	342	0.826	29.237	34.652	1.00	27.76	6
ATOM	453	NZ	LYS	342	1.671	29.690	33.538	1.00	27.89	7
ATOM	454	C	LYS	342	0.031	33.147	38.416	1.00	25.41	6
ATOM	455	O	LYS	342	-0.925	33.562	37.759	1.00	25.80	8
ATOM	456	N	LYS	343	0.040	33.143	39.741	1.00	25.92	7
ATOM	457	CA	LYS	343	-1.134	33.579	40.464	1.00	29.28	6
ATOM	458	CB	LYS	343	-1.684	32.396	41.289	1.00	30.55	6
ATOM	459	CG	LYS	343	-2.177	31.209	40.428	1.00	34.94	6
ATOM	460	CD	LYS	343	-2.189	29.909	41.276	1.00	38.00	6
ATOM	461	CE	LYS	343	-2.844	28.710	40.539	1.00	42.13	6
ATOM	462	NZ	LYS	343	-4.264	29.048	40.111	1.00	45.88	7
ATOM	463	C	LYS	343	-0.973	34.821	41.327	1.00	29.54	6
ATOM	464	O	LYS	343	-1.937	35.623	41.337	1.00	30.97	8
ATOM	465	N	LEU	344	0.186	35.012	41.973	1.00	29.12	7
ATOM	466	CA	LEU	344	0.409	36.153	42.846	1.00	30.88	6
ATOM	467	CB	LEU	344	1.427	35.842	44.008	1.00	33.60	6
ATOM	468	CG	LEU	344	0.966	35.142	45.315	1.00	36.84	6
ATOM	469	CD1	LEU	344	1.439	35.838	46.518	1.00	38.66	6
ATOM	470	CD2	LEU	344	-0.453	35.289	45.496	1.00	37.58	6
ATOM	471	C	LEU	344	1.050	37.348	42.159	1.00	29.59	6
ATOM	472	O	LEU	344	2.090	37.211	41.470	1.00	27.82	8
ATOM	473	N	PRO	345	0.459	38.567	42.427	1.00	31.73	7
ATOM	474	CD	PRO	345	-0.782	38.971	43.119	1.00	30.83	6
ATOM	475	CA	PRO	345	1.058	39.747	41.821	1.00	32.80	6
ATOM	476	CB	PRO	345	0.109	40.882	42.162	1.00	32.28	6
ATOM	477	CG	PRO	345	-0.663	40.499	43.278	1.00	32.28	6
ATOM	478	C	PRO	345	2.406	39.957	42.437	1.00	35.91	6
ATOM	479	O	PRO	345	2.634	39.519	43.614	1.00	35.86	8
ATOM	480	N	SER	346	3.334	40.501	41.648	1.00	39.68	7
ATOM	481	CA	SER	346	4.637	40.670	42.251	1.00	43.69	6

ATOM	482	CB	SER	346	5.738	41.300	41.367	1.00	44.35	6
ATOM	483	OG	SER	346	5.957	40.576	40.195	1.00	45.03	8
ATOM	484	C	SER	346	4.663	41.551	43.477	1.00	46.72	6
ATOM	485	O	SER	346	5.772	41.833	43.906	1.00	49.01	8
ATOM	486	N	GLY	347	3.864	41.890	44.052	1.00	48.86	7
ATOM	487	CA	GLY	347	3.901	42.777	45.174	1.00	51.37	6
ATOM	488	C	GLY	347	3.693	42.029	46.475	1.00	51.01	6
ATOM	489	O	GLY	347	3.343	42.624	47.516	1.00	51.80	8
ATOM	490	N	HIS	348	2.705	41.076	46.101	1.00	49.68	7
ATOM	491	CA	HIS	348	2.235	40.289	47.237	1.00	49.33	6
ATOM	492	C	HIS	348	3.289	39.274	47.657	1.00	49.31	6
ATOM	493	O	HIS	348	3.321	38.722	48.607	1.00	49.10	8
ATOM	494	CB	HIS	348	0.940	39.527	46.888	1.00	50.03	6
ATOM	495	CG	HIS	348	-0.240	40.445	46.482	1.00	52.00	6
ATOM	496	ND1	HIS	348	-0.901	41.250	47.385	1.00	20.00	7
ATOM	497	CD2	HIS	348	-0.836	40.652	45.285	1.00	20.00	6
ATOM	498	CE1	HIS	348	-1.856	41.916	46.759	1.00	20.00	6
ATOM	499	NE2	HIS	348	-1.838	41.571	45.484	1.00	20.00	7
ATOM	500	N	SER	349	4.229	39.205	46.618	1.00	48.97	7
ATOM	501	CA	SER	349	5.367	38.283	46.822	1.00	48.03	6
ATOM	502	CB	SER	349	5.975	37.696	45.538	1.00	49.59	6
ATOM	503	OG	SER	349	5.094	36.756	44.992	1.00	52.99	8
ATOM	504	C	SER	349	6.461	38.889	47.588	1.00	46.83	6
ATOM	505	O	SER	349	6.999	38.247	48.490	1.00	45.12	8
ATOM	506	N	ASP	350	6.808	40.129	47.266	1.00	45.53	7
ATOM	507	CA	ASP	350	7.881	40.775	48.049	1.00	44.40	6
ATOM	508	CB	ASP	350	8.338	42.169	47.430	1.00	46.18	6
ATOM	509	CG	ASP	350	8.245	42.222	45.811	1.00	48.32	6
ATOM	510	OD1	ASP	350	8.264	41.151	45.237	1.00	48.97	8
ATOM	511	OD2	ASP	350	8.174	43.288	45.086	1.00	49.98	8
ATOM	512	C	ASP	350	7.358	40.943	49.512	1.00	42.08	6
ATOM	513	O	ASP	350	8.132	41.063	50.450	1.00	41.23	8
ATOM	514	N	LEU	351	6.046	41.001	49.671	1.00	40.76	7
ATOM	515	CA	LEU	351	5.454	41.102	50.966	1.00	39.24	6
ATOM	516	CB	LEU	351	4.040	41.556	50.828	1.00	40.26	6
ATOM	517	CG	LEU	351	3.970	43.030	51.263	1.00	43.57	6
ATOM	518	CD1	LEU	351	5.191	43.868	50.777	1.00	44.27	6
ATOM	519	CD2	LEU	351	2.672	43.599	50.735	1.00	42.89	6
ATOM	520	C	LEU	351	5.528	39.757	51.703	1.00	38.55	6
ATOM	521	O	LEU	351	5.700	39.682	52.916	1.00	36.15	8
ATOM	522	N	LEU	352	5.394	38.661	50.964	1.00	35.86	7
ATOM	523	CA	LEU	352	5.479	37.336	51.587	1.00	34.36	6
ATOM	524	CB	LEU	352	4.861	36.224	50.695	1.00	36.39	6
ATOM	525	CG	LEU	352	3.607	35.615	51.310	1.00	38.73	6
ATOM	526	CD1	LEU	352	2.617	36.628	51.792	1.00	40.40	6
ATOM	527	CD2	LEU	352	3.022	34.774	50.199	1.00	39.17	6
ATOM	528	C	LEU	352	6.924	37.010	51.959	1.00	33.09	6
ATOM	529	O	LEU	352	7.161	36.388	52.999	1.00	31.06	8
ATOM	530	N	GLU	353	7.879	37.476	51.155	1.00	32.12	7
ATOM	531	CA	GLU	353	9.299	37.261	51.445	1.00	34.04	6
ATOM	532	CB	GLU	353	10.189	37.765	50.301	1.00	35.06	6
ATOM	533	CG	GLU	353	11.677	37.679	50.629	1.00	38.80	6
ATOM	534	CD	GLU	353	12.559	38.117	49.473	1.00	41.58	6
ATOM	535	OE1	GLU	353	12.415	37.601	48.369	1.00	44.58	8
ATOM	536	OE2	GLU	353	13.419	38.988	49.632	1.00	44.72	8
ATOM	537	C	GLU	353	9.725	37.983	52.736	1.00	34.22	6
ATOM	538	O	GLU	353	10.557	37.493	53.513	1.00	32.47	8
ATOM	539	N	GLU	354	9.098	39.204	52.963	1.00	33.64	7

ATOM	540	CA	GLU	354	9.410	40.097	54.063	1.00	35.11	6
ATOM	541	CB	GLU	354	8.910	41.506	53.712	1.00	37.91	6
ATOM	542	CG	GLU	354	9.030	42.544	54.805	1.00	42.37	6
ATOM	543	CD	GLU	354	7.846	43.504	54.803	1.00	45.04	6
ATOM	544	OE1	GLU	354	8.026	44.610	54.232	1.00	48.51	8
ATOM	545	OE2	GLU	354	6.750	43.150	55.341	1.00	44.43	8
ATOM	546	C	GLU	354	8.697	39.549	55.277	1.00	33.30	6
ATOM	547	O	GLU	354	9.291	39.453	56.351	1.00	34.63	8
ATOM	548	N	ARG	355	7.616	38.768	55.113	1.00	31.81	7
ATOM	549	CA	ARG	355	6.901	38.090	56.172	1.00	32.49	6
ATOM	550	CB	ARG	355	5.511	37.716	55.676	1.00	35.34	6
ATOM	551	CG	ARG	355	4.679	36.915	56.673	1.00	38.68	6
ATOM	552	CD	ARG	355	4.309	37.797	57.855	1.00	42.55	6
ATOM	553	NE	ARG	355	4.063	37.012	59.057	1.00	44.20	7
ATOM	554	CZ	ARG	355	5.002	36.544	59.877	1.00	46.76	6
ATOM	555	NH1	ARG	355	6.306	36.764	59.656	1.00	45.35	7
ATOM	556	NH2	ARG	355	4.616	35.864	60.962	1.00	50.30	7
ATOM	557	C	ARG	355	7.651	36.842	56.615	1.00	32.79	6
ATOM	558	O	ARG	355	7.843	36.597	57.804	1.00	31.25	8
ATOM	559	N	ILE	356	8.115	36.037	55.662	1.00	31.30	7
ATOM	560	CA	ILE	356	8.802	34.818	56.066	1.00	31.81	6
ATOM	561	CB	ILE	356	8.906	33.776	54.868	1.00	29.87	6
ATOM	562	CG2	ILE	356	10.063	34.169	53.868	1.00	29.78	6
ATOM	563	CG1	ILE	356	9.220	32.361	55.437	1.00	31.98	6
ATOM	564	CD1	ILE	356	9.226	31.168	54.362	1.00	27.51	6
ATOM	565	C	ILE	356	10.205	35.055	56.638	1.00	32.66	6
ATOM	566	O	ILE	356	10.641	34.346	57.572	1.00	30.28	8
ATOM	567	N	ARG	357	10.962	36.020	56.110	1.00	34.98	7
ATOM	568	CA	ARG	357	12.324	36.200	56.661	1.00	38.93	6
ATOM	569	CB	ARG	357	13.159	37.184	55.843	1.00	39.92	6
ATOM	570	CG	ARG	357	12.510	38.453	55.500	1.00	42.64	6
ATOM	571	CD	ARG	357	13.332	39.115	54.358	1.00	45.19	6
ATOM	572	NE	ARG	357	14.636	38.470	54.098	1.00	47.06	7
ATOM	573	CZ	ARG	357	14.809	37.390	53.331	1.00	47.03	6
ATOM	574	NH1	ARG	357	13.744	36.855	52.769	1.00	48.06	7
ATOM	575	NH2	ARG	357	16.018	36.857	53.109	1.00	45.38	7
ATOM	576	C	ARG	357	12.088	36.712	58.082	1.00	40.92	6
ATOM	577	O	ARG	357	12.957	36.459	58.964	1.00	43.42	8
ATOM	578	N	ASN	358	11.002	37.390	58.441	1.00	41.89	7
ATOM	579	CA	ASN	358	10.992	37.671	59.865	1.00	44.29	6
ATOM	580	CB	ASN	358	10.905	39.179	60.259	1.00	46.14	6
ATOM	581	CG	ASN	358	10.651	40.122	59.091	1.00	47.37	6
ATOM	582	OD1	ASN	358	11.577	40.644	58.467	1.00	48.97	8
ATOM	583	ND2	ASN	358	9.374	40.390	58.818	1.00	49.43	7
ATOM	584	C	ASN	358	9.816	36.877	60.504	1.00	45.02	6
ATOM	585	O	ASN	358	8.747	37.439	60.975	1.00	47.50	8
ATOM	586	N	SER	359	10.004	35.549	60.466	1.00	43.44	7
ATOM	587	CA	SER	359	9.093	34.575	61.063	1.00	40.81	6
ATOM	588	CB	SER	359	8.335	33.776	60.022	1.00	41.60	6
ATOM	589	OG	SER	359	9.197	32.797	59.453	1.00	39.14	8
ATOM	590	C	SER	359	9.934	33.552	61.867	1.00	39.57	6
ATOM	591	O	SER	359	9.379	32.681	62.527	1.00	40.17	8
ATOM	592	N	GLY	360	11.257	33.644	61.822	1.00	36.41	7
ATOM	593	CA	GLY	360	12.063	32.691	62.550	1.00	36.02	6
ATOM	594	C	GLY	360	12.873	31.891	61.531	1.00	35.83	6
ATOM	595	O	GLY	360	14.065	31.652	61.730	1.00	36.26	8
ATOM	596	N	ILE	361	12.254	31.521	60.407	1.00	34.21	7
ATOM	597	CA	ILE	361	12.982	30.741	59.391	1.00	32.82	6

ATOM	598	CB	ILE	361	12.060	30.426	58.203	1.00	31.34	6
ATOM	599	CG2	ILE	361	12.842	29.799	57.081	1.00	30.21	6
ATOM	600	CG1	ILE	361	10.917	29.558	58.717	1.00	30.43	6
ATOM	601	CD1	ILE	361	9.860	29.175	57.726	1.00	28.64	6
ATOM	602	C	ILE	361	14.168	31.561	58.947	1.00	32.20	6
ATOM	603	O	ILE	361	14.066	32.747	58.853	1.00	31.99	8
ATOM	604	N	SER	362	15.249	30.865	58.422	1.00	32.80	7
ATOM	605	CA	SER	362	16.369	31.700	58.062	1.00	35.78	6
ATOM	606	CB	SER	362	17.628	31.137	58.707	1.00	37.94	6
ATOM	607	OG	SER	362	18.036	29.990	57.973	1.00	40.33	8
ATOM	608	C	SER	362	16.616	31.780	56.571	1.00	36.80	6
ATOM	609	O	SER	362	15.879	31.174	55.756	1.00	34.55	8
ATOM	610	N	ASP	363	17.755	32.570	56.446	1.00	37.56	7
ATOM	611	CA	ASP	363	18.328	32.538	55.124	1.00	39.66	6
ATOM	612	CB	ASP	363	19.507	33.511	55.002	1.00	42.07	6
ATOM	613	CG	ASP	363	19.120	34.788	54.334	1.00	45.41	6
ATOM	614	OD1	ASP	363	18.656	34.743	53.162	1.00	47.71	8
ATOM	615	OD2	ASP	363	19.266	35.852	54.984	1.00	48.83	8
ATOM	616	C	ASP	363	18.821	31.089	54.995	1.00	39.22	6
ATOM	617	O	ASP	363	18.580	30.256	55.861	1.00	41.99	8
ATOM	618	N	GLU	364	19.548	30.769	53.958	1.00	38.05	7
ATOM	619	CA	GLU	364	19.946	29.390	53.787	1.00	36.18	6
ATOM	620	CB	GLU	364	20.572	28.816	55.051	1.00	39.36	6
ATOM	621	CG	GLU	364	21.934	28.199	54.764	1.00	45.91	6
ATOM	622	CD	GLU	364	22.741	27.977	56.034	1.00	49.50	6
ATOM	623	OE1	GLU	364	22.208	27.315	56.953	1.00	53.22	8
ATOM	624	OE2	GLU	364	23.900	28.458	56.134	1.00	52.53	8
ATOM	625	C	GLU	364	18.703	28.611	53.339	1.00	31.82	6
ATOM	626	O	GLU	364	18.831	27.751	52.487	1.00	30.82	8
ATOM	627	N	TYR	365	17.518	28.929	53.893	1.00	28.83	7
ATOM	628	CA	TYR	365	16.250	28.298	53.427	1.00	27.58	6
ATOM	629	CB	TYR	365	15.298	28.036	54.585	1.00	25.28	6
ATOM	630	CG	TYR	365	14.061	27.273	54.172	1.00	22.64	6
ATOM	631	CD1	TYR	365	14.118	25.899	53.916	1.00	20.67	6
ATOM	632	CE1	TYR	365	12.954	25.163	53.636	1.00	21.27	6
ATOM	633	CD2	TYR	365	12.816	27.903	54.116	1.00	20.43	6
ATOM	634	CE2	TYR	365	11.625	27.191	53.824	1.00	18.96	6
ATOM	635	CZ	TYR	365	11.700	25.813	53.599	1.00	19.07	6
ATOM	636	OH	TYR	365	10.598	24.974	53.454	1.00	20.64	8
ATOM	637	C	TYR	365	15.512	29.263	52.448	1.00	26.08	6
ATOM	638	O	TYR	365	15.147	28.901	51.314	1.00	24.75	8
ATOM	639	N	ILE	366	15.302	30.494	52.899	1.00	26.17	7
ATOM	640	CA	ILE	366	14.568	31.514	52.123	1.00	27.29	6
ATOM	641	CB	ILE	366	14.326	32.737	52.951	1.00	26.78	6
ATOM	642	CG2	ILE	366	13.620	33.832	52.098	1.00	26.70	6
ATOM	643	CG1	ILE	366	13.508	32.332	54.189	1.00	27.76	6
ATOM	644	CD1	ILE	366	13.402	33.410	55.257	1.00	26.95	6
ATOM	645	C	ILE	366	15.214	31.909	50.810	1.00	28.05	6
ATOM	646	O	ILE	366	14.543	31.975	49.787	1.00	28.30	8
ATOM	647	N	THR	367	16.519	32.153	50.839	1.00	28.47	7
ATOM	648	CA	THR	367	17.256	32.499	49.628	1.00	27.70	6
ATOM	649	CB	THR	367	18.702	32.802	49.938	1.00	31.22	6
ATOM	650	OG1	THR	367	18.759	34.128	50.481	1.00	34.14	8
ATOM	651	CG2	THR	367	19.602	32.659	48.659	1.00	31.67	6
ATOM	652	C	THR	367	17.184	31.477	48.512	1.00	26.16	6
ATOM	653	O	THR	367	16.935	31.841	47.372	1.00	25.50	8
ATOM	654	N	PRO	368	17.434	30.189	48.799	1.00	23.54	7
ATOM	655	CD	PRO	368	17.966	29.604	50.036	1.00	24.08	6

ATOM	656	CA	PRO	368	17.342	29.195	47.733	1.00	20.99	6
ATOM	657	CB	PRO	368	17.791	27.884	48.421	1.00	23.25	6
ATOM	658	CG	PRO	368	18.717	28.387	49.540	1.00	25.50	6
ATOM	659	C	PRO	368	15.867	29.144	47.309	1.00	18.85	6
ATOM	660	O	PRO	368	15.577	28.973	46.130	1.00	18.28	8
ATOM	661	N	MET	369	14.951	29.252	48.271	1.00	16.87	7
ATOM	662	CA	MET	369	13.519	29.254	47.932	1.00	18.73	6
ATOM	663	CB	MET	369	12.668	29.686	49.110	1.00	17.86	6
ATOM	664	CG	MET	369	11.198	29.784	48.779	1.00	17.41	6
ATOM	665	SD	MET	369	10.297	30.313	50.291	1.00	22.80	16
ATOM	666	CE	MET	369	9.850	28.817	50.943	1.00	18.91	6
ATOM	667	C	MET	369	13.210	30.249	46.795	1.00	20.73	6
ATOM	668	O	MET	369	12.695	29.871	45.734	1.00	21.58	8
ATOM	669	N	PHE	370	13.500	31.534	47.040	1.00	22.10	7
ATOM	670	CA	PHE	370	13.169	32.537	46.019	1.00	23.21	6
ATOM	671	CB	PHE	370	13.182	33.971	46.582	1.00	22.60	6
ATOM	672	CG	PHE	370	11.994	34.278	47.453	1.00	23.31	6
ATOM	673	CD1	PHE	370	11.971	33.925	48.823	1.00	25.56	6
ATOM	674	CD2	PHE	370	10.893	34.875	46.921	1.00	24.85	6
ATOM	675	CE1	PHE	370	10.828	34.196	49.605	1.00	24.07	6
ATOM	676	CE2	PHE	370	9.777	35.145	47.666	1.00	25.17	6
ATOM	677	CZ	PHE	370	9.730	34.811	49.021	1.00	27.62	6
ATOM	678	C	PHE	370	14.026	32.439	44.783	1.00	23.76	6
ATOM	679	O	PHE	370	13.597	32.803	43.690	1.00	24.18	8
ATOM	680	N	SER	371	15.251	31.979	44.945	1.00	23.62	7
ATOM	681	CA	SER	371	16.091	31.825	43.784	1.00	23.74	6
ATOM	682	CB	SER	371	17.455	31.340	44.250	1.00	25.68	6
ATOM	683	OG	SER	371	18.336	31.438	43.153	1.00	29.39	8
ATOM	684	C	SER	371	15.387	30.771	42.868	1.00	21.96	6
ATOM	685	O	SER	371	15.272	30.944	41.613	1.00	19.76	8
ATOM	686	N	PHE	372	14.928	29.676	43.480	1.00	18.27	7
ATOM	687	CA	PHE	372	14.240	28.664	42.690	1.00	18.05	6
ATOM	688	CB	PHE	372	13.861	27.453	43.557	1.00	17.30	6
ATOM	689	CG	PHE	372	12.999	26.482	42.852	1.00	18.83	6
ATOM	690	CD1	PHE	372	13.564	25.676	41.885	1.00	18.36	6
ATOM	691	CD2	PHE	372	11.659	26.326	43.194	1.00	18.44	6
ATOM	692	CE1	PHE	372	12.839	24.709	41.262	1.00	22.71	6
ATOM	693	CE2	PHE	372	10.910	25.340	42.571	1.00	20.16	6
ATOM	694	CZ	PHE	372	11.506	24.527	41.603	1.00	19.39	6
ATOM	695	C	PHE	372	12.957	29.232	41.991	1.00	19.15	6
ATOM	696	O	PHE	372	12.736	28.949	40.788	1.00	18.15	8
ATOM	697	N	TYR	373	12.125	30.010	42.707	1.00	18.39	7
ATOM	698	CA	TYR	373	10.894	30.569	42.119	1.00	19.57	6
ATOM	699	CB	TYR	373	10.156	31.477	43.107	1.00	18.29	6
ATOM	700	CG	TYR	373	9.584	30.790	44.316	1.00	19.02	6
ATOM	701	CD1	TYR	373	9.342	29.421	44.318	1.00	19.27	6
ATOM	702	CE1	TYR	373	8.755	28.821	45.402	1.00	19.82	6
ATOM	703	CD2	TYR	373	9.226	31.532	45.467	1.00	18.64	6
ATOM	704	CE2	TYR	373	8.651	30.918	46.589	1.00	19.78	6
ATOM	705	CZ	TYR	373	8.417	29.563	46.544	1.00	19.87	6
ATOM	706	OH	TYR	373	7.908	28.880	47.640	1.00	18.83	8
ATOM	707	C	TYR	373	11.238	31.384	40.854	1.00	21.91	6
ATOM	708	O	TYR	373	10.561	31.281	39.818	1.00	20.54	8
ATOM	709	N	LYS	374	12.327	32.145	40.934	1.00	23.61	7
ATOM	710	CA	LYS	374	12.775	32.948	39.790	1.00	26.50	6
ATOM	711	CB	LYS	374	13.960	33.868	40.173	1.00	29.49	6
ATOM	712	CG	LYS	374	13.629	34.909	41.229	1.00	35.57	6
ATOM	713	CD	LYS	374	12.595	35.878	40.618	1.00	40.48	6

ATOM	714	CE	LYS	374	12.285	35.575	39.126	1.00	43.83	6
ATOM	715	NZ	LYS	374	10.831	35.197	38.902	1.00	44.66	7
ATOM	716	C	LYS	374	13.266	32.020	38.727	1.00	25.35	6
ATOM	717	O	LYS	374	12.903	32.144	37.548	1.00	26.16	8
ATOM	718	N	SER	375	14.097	31.070	39.132	1.00	25.05	7
ATOM	719	CA	SER	375	14.687	30.172	38.181	1.00	24.04	6
ATOM	720	CB	SER	375	15.594	29.188	38.901	1.00	24.76	6
ATOM	721	OG	SER	375	16.090	28.224	37.984	1.00	24.17	8
ATOM	722	C	SER	375	13.700	29.422	37.313	1.00	25.83	6
ATOM	723	O	SER	375	13.840	29.370	36.080	1.00	26.22	8
ATOM	724	N	ILE	376	12.686	28.835	37.939	1.00	25.43	7
ATOM	725	CA	ILE	376	11.720	28.073	37.169	1.00	25.67	6
ATOM	726	CB	ILE	376	10.976	27.026	38.017	1.00	27.81	6
ATOM	727	CG2	ILE	376	10.050	27.704	39.019	1.00	26.42	6
ATOM	728	CG1	ILE	376	10.193	26.099	37.086	1.00	30.85	6
ATOM	729	CD1	ILE	376	9.769	24.773	37.754	1.00	32.32	6
ATOM	730	C	ILE	376	10.769	29.056	36.487	1.00	23.70	6
ATOM	731	O	ILE	376	10.244	28.765	35.428	1.00	23.13	8
ATOM	732	N	GLY	377	10.605	30.244	37.051	1.00	22.29	7
ATOM	733	CA	GLY	377	9.765	31.233	36.391	1.00	21.42	6
ATOM	734	C	GLY	377	10.311	31.632	35.008	1.00	21.64	6
ATOM	735	O	GLY	377	9.567	32.070	34.096	1.00	20.06	8
ATOM	736	N	GLU	378	11.638	31.510	34.847	1.00	23.21	7
ATOM	737	CA	GLU	378	12.284	31.790	33.536	1.00	24.44	6
ATOM	738	CB	GLU	378	13.812	31.687	33.624	1.00	24.68	6
ATOM	739	CG	GLU	378	14.433	32.792	34.397	1.00	29.72	6
ATOM	740	CD	GLU	378	15.949	32.580	34.571	1.00	34.23	6
ATOM	741	OE1	GLU	378	16.582	32.004	33.647	1.00	33.28	8
ATOM	742	OE2	GLU	378	16.497	33.008	35.625	1.00	36.12	8
ATOM	743	C	GLU	378	11.828	30.790	32.471	1.00	24.16	6
ATOM	744	O	GLU	378	11.945	31.051	31.284	1.00	23.87	8
ATOM	745	N	LEU	379	11.351	29.627	32.856	1.00	23.79	7
ATOM	746	CA	LEU	379	10.916	28.690	31.810	1.00	25.23	6
ATOM	747	CB	LEU	379	11.001	27.278	32.392	1.00	24.01	6
ATOM	748	CG	LEU	379	12.448	26.867	32.758	1.00	27.85	6
ATOM	749	CD1	LEU	379	12.496	25.459	33.132	1.00	26.09	6
ATOM	750	CD2	LEU	379	13.415	27.024	31.537	1.00	26.52	6
ATOM	751	C	LEU	379	9.466	29.007	31.260	1.00	23.19	6
ATOM	752	O	LEU	379	8.988	28.400	30.296	1.00	23.76	8
ATOM	753	N	LYS	380	8.775	29.929	31.901	1.00	22.23	7
ATOM	754	CA	LYS	380	7.420	30.287	31.482	1.00	25.06	6
ATOM	755	CB	LYS	380	7.496	31.160	30.231	1.00	26.20	6
ATOM	756	CG	LYS	380	8.485	32.294	30.380	1.00	30.84	6
ATOM	757	CD	LYS	380	8.321	33.260	29.190	1.00	35.79	6
ATOM	758	CE	LYS	380	9.401	34.374	29.158	1.00	39.66	6
ATOM	759	NZ	LYS	380	10.649	34.032	28.365	1.00	40.21	7
ATOM	760	C	LYS	380	6.550	29.036	31.194	1.00	23.61	6
ATOM	761	O	LYS	380	5.897	28.935	30.164	1.00	22.42	8
ATOM	762	N	MET	381	6.551	28.078	32.113	1.00	21.57	7
ATOM	763	CA	MET	381	5.760	26.880	31.855	1.00	21.39	6
ATOM	764	CB	MET	381	6.153	25.794	32.861	1.00	21.45	6
ATOM	765	CG	MET	381	7.626	25.398	32.836	1.00	25.21	6
ATOM	766	SD	MET	381	8.005	24.440	34.325	1.00	27.43	16
ATOM	767	CE	MET	381	6.658	23.493	34.392	1.00	27.50	6
ATOM	768	C	MET	381	4.241	27.093	31.873	1.00	19.99	6
ATOM	769	O	MET	381	3.749	27.935	32.608	1.00	20.28	8
ATOM	770	N	THR	382	3.502	26.368	31.030	1.00	20.88	7
ATOM	771	CA	THR	382	2.042	26.463	31.049	1.00	19.14	6

ATOM	772	CB	THR	382	1.396	25.889	29.766	1.00	19.39	6
ATOM	773	OG1	THR	382	1.688	24.482	29.676	1.00	18.31	8
ATOM	774	CG2	THR	382	1.939	26.614	28.521	1.00	18.66	6
ATOM	775	C	THR	382	1.555	25.594	32.228	1.00	19.36	6
ATOM	776	O	THR	382	2.344	24.816	32.841	1.00	17.49	8
ATOM	777	N	GLN	383	0.276	25.751	32.567	1.00	17.92	7
ATOM	778	CA	GLN	383	-0.334	24.948	33.641	1.00	19.83	6
ATOM	779	CB	GLN	383	-1.828	25.320	33.813	1.00	21.28	6
ATOM	780	CG	GLN	383	-2.494	24.698	35.094	1.00	28.08	6
ATOM	781	CD	GLN	383	-4.076	24.726	35.091	1.00	32.74	6
ATOM	782	OE1	GLN	383	-4.735	24.870	36.153	1.00	35.35	8
ATOM	783	NE2	GLN	383	-4.674	24.565	33.897	1.00	31.92	7
ATOM	784	C	GLN	383	-0.204	23.437	33.252	1.00	18.37	6
ATOM	785	O	GLN	383	0.004	22.589	34.121	1.00	18.49	8
ATOM	786	N	GLU	384	-0.334	23.113	31.960	1.00	18.33	7
ATOM	787	CA	GLU	384	-0.190	21.710	31.563	1.00	19.34	6
ATOM	788	CB	GLU	384	-0.505	21.513	30.049	1.00	20.07	6
ATOM	789	CG	GLU	384	-2.000	21.770	29.745	1.00	22.34	6
ATOM	790	CD	GLU	384	-2.319	21.706	28.236	1.00	25.69	6
ATOM	791	OE1	GLU	384	-1.413	21.884	27.427	1.00	26.17	8
ATOM	792	OE2	GLU	384	-3.483	21.458	27.837	1.00	26.85	8
ATOM	793	C	GLU	384	1.220	21.216	31.895	1.00	19.98	6
ATOM	794	O	GLU	384	1.373	20.114	32.432	1.00	17.01	8
ATOM	795	N	GLU	385	2.243	22.028	31.587	1.00	17.80	7
ATOM	796	CA	GLU	385	3.611	21.631	31.918	1.00	17.45	6
ATOM	797	CB	GLU	385	4.608	22.649	31.378	1.00	16.42	6
ATOM	798	CG	GLU	385	4.738	22.522	29.860	1.00	18.03	6
ATOM	799	CD	GLU	385	5.280	23.818	29.336	1.00	19.59	6
ATOM	800	OE1	GLU	385	4.486	24.766	29.074	1.00	20.92	8
ATOM	801	OE2	GLU	385	6.518	23.916	29.271	1.00	19.49	8
ATOM	802	C	GLU	385	3.815	21.454	33.435	1.00	17.61	6
ATOM	803	O	GLU	385	4.403	20.437	33.863	1.00	17.28	8
ATOM	804	N	TYR	386	3.307	22.379	34.244	1.00	15.40	7
ATOM	805	CA	TYR	386	3.476	22.193	35.696	1.00	16.28	6
ATOM	806	CB	TYR	386	2.891	23.349	36.504	1.00	17.10	6
ATOM	807	CG	TYR	386	3.846	24.483	36.745	1.00	18.99	6
ATOM	808	CD1	TYR	386	4.756	24.427	37.766	1.00	20.84	6
ATOM	809	CE1	TYR	386	5.563	25.515	38.051	1.00	23.05	6
ATOM	810	CD2	TYR	386	3.766	25.643	35.998	1.00	20.35	6
ATOM	811	CE2	TYR	386	4.574	26.752	36.268	1.00	22.60	6
ATOM	812	CZ	TYR	386	5.471	26.669	37.288	1.00	24.26	6
ATOM	813	OH	TYR	386	6.346	27.711	37.535	1.00	27.07	8
ATOM	814	C	TYR	386	2.779	20.928	36.170	1.00	16.40	6
ATOM	815	O	TYR	386	3.287	20.239	37.044	1.00	17.66	8
ATOM	816	N	ALA	387	1.566	20.674	35.671	1.00	14.81	7
ATOM	817	CA	ALA	387	0.813	19.485	36.115	1.00	14.98	6
ATOM	818	CB	ALA	387	-0.628	19.413	35.429	1.00	15.82	6
ATOM	819	C	ALA	387	1.604	18.189	35.794	1.00	15.05	6
ATOM	820	O	ALA	387	1.722	17.313	36.676	1.00	14.49	8
ATOM	821	N	LEU	388	2.095	18.066	34.560	1.00	14.72	7
ATOM	822	CA	LEU	388	2.863	16.875	34.167	1.00	16.46	6
ATOM	823	CB	LEU	388	3.152	16.869	32.657	1.00	15.66	6
ATOM	824	CG	LEU	388	2.117	16.161	31.748	1.00	18.69	6
ATOM	825	CD1	LEU	388	2.223	14.619	31.987	1.00	20.30	6
ATOM	826	CD2	LEU	388	0.720	16.613	32.125	1.00	21.34	6
ATOM	827	C	LEU	388	4.198	16.797	34.959	1.00	15.98	6
ATOM	828	O	LEU	388	4.602	15.689	35.404	1.00	13.29	8
ATOM	829	N	LEU	389	4.871	17.940	35.144	1.00	15.33	7

ATOM	830	CA	LEU	389	6.137	17.834	35.890	1.00	14.94	6
ATOM	831	CB	LEU	389	6.889	19.144	35.896	1.00	15.79	6
ATOM	832	CG	LEU	389	8.331	19.047	36.364	1.00	17.32	6
ATOM	833	CD1	LEU	389	9.131	18.227	35.343	1.00	16.03	6
ATOM	834	CD2	LEU	389	8.907	20.478	36.485	1.00	18.51	6
ATOM	835	C	LEU	389	5.883	17.357	37.334	1.00	14.12	6
ATOM	836	O	LEU	389	6.661	16.572	37.903	1.00	13.80	8
ATOM	837	N	THR	390	4.762	17.795	37.898	1.00	15.10	7
ATOM	838	CA	THR	390	4.366	17.410	39.272	1.00	13.91	6
ATOM	839	CB	THR	390	3.134	18.231	39.748	1.00	14.30	6
ATOM	840	OG1	THR	390	3.494	19.637	39.696	1.00	18.36	8
ATOM	841	CG2	THR	390	2.743	17.859	41.249	1.00	13.78	6
ATOM	842	C	THR	390	4.053	15.893	39.327	1.00	14.21	6
ATOM	843	O	THR	390	4.470	15.213	40.234	1.00	15.26	8
ATOM	844	N	ALA	391	3.308	15.378	38.355	1.00	14.62	7
ATOM	845	CA	ALA	391	3.014	13.968	38.293	1.00	13.24	6
ATOM	846	CB	ALA	391	2.107	13.713	37.113	1.00	15.33	6
ATOM	847	C	ALA	391	4.345	13.187	38.118	1.00	14.72	6
ATOM	848	O	ALA	391	4.548	12.133	38.751	1.00	13.37	8
ATOM	849	N	ILE	392	5.247	13.684	37.287	1.00	13.13	7
ATOM	850	CA	ILE	392	6.575	12.963	37.092	1.00	16.12	6
ATOM	851	CB	ILE	392	7.328	13.614	35.949	1.00	14.45	6
ATOM	852	CG2	ILE	392	8.827	13.191	35.901	1.00	16.87	6
ATOM	853	CG1	ILE	392	6.602	13.233	34.678	1.00	16.27	6
ATOM	854	CD1	ILE	392	7.091	14.136	33.490	1.00	18.18	6
ATOM	855	C	ILE	392	7.436	12.934	38.355	1.00	16.58	6
ATOM	856	O	ILE	392	8.092	11.928	38.676	1.00	16.99	8
ATOM	857	N	VAL	393	7.400	14.044	39.082	1.00	16.17	7
ATOM	858	CA	VAL	393	8.091	14.125	40.352	1.00	17.56	6
ATOM	859	CB	VAL	393	7.958	15.503	40.998	1.00	18.35	6
ATOM	860	CG1	VAL	393	8.519	15.440	42.409	1.00	21.30	6
ATOM	861	CG2	VAL	393	8.731	16.591	40.195	1.00	20.45	6
ATOM	862	C	VAL	393	7.469	13.106	41.345	1.00	17.21	6
ATOM	863	O	VAL	393	8.206	12.442	42.077	1.00	14.47	8
ATOM	864	N	ILE	394	6.129	12.993	41.410	1.00	15.70	7
ATOM	865	CA	ILE	394	5.516	12.068	42.391	1.00	15.27	6
ATOM	866	CB	ILE	394	3.964	12.310	42.490	1.00	15.62	6
ATOM	867	CG2	ILE	394	3.302	11.247	43.332	1.00	12.98	6
ATOM	868	CG1	ILE	394	3.681	13.714	43.071	1.00	17.17	6
ATOM	869	CD1	ILE	394	2.279	14.186	42.757	1.00	14.90	6
ATOM	870	C	ILE	394	5.820	10.592	42.007	1.00	16.06	6
ATOM	871	O	ILE	394	6.180	9.737	42.863	1.00	14.53	8
ATOM	872	N	LEU	395	5.652	10.292	40.738	1.00	14.10	7
ATOM	873	CA	LEU	395	5.976	8.961	40.244	1.00	15.38	6
ATOM	874	CB	LEU	395	5.072	8.678	39.080	1.00	14.05	6
ATOM	875	CG	LEU	395	3.571	8.648	39.384	1.00	16.30	6
ATOM	876	CD1	LEU	395	2.856	8.626	37.994	1.00	16.58	6
ATOM	877	CD2	LEU	395	3.193	7.350	40.234	1.00	18.82	6
ATOM	878	C	LEU	395	7.493	8.747	39.897	1.00	16.08	6
ATOM	879	O	LEU	395	7.856	8.285	38.774	1.00	14.33	8
ATOM	880	N	SER	396	8.359	9.006	40.897	1.00	16.14	7
ATOM	881	CA	SER	396	9.819	8.857	40.770	1.00	18.25	6
ATOM	882	CB	SER	396	10.591	9.879	41.642	1.00	18.93	6
ATOM	883	OG	SER	396	10.309	11.194	41.187	1.00	22.70	8
ATOM	884	C	SER	396	10.229	7.446	41.175	1.00	17.49	6
ATOM	885	O	SER	396	10.095	7.050	42.329	1.00	17.49	8
ATOM	886	N	PRO	397	10.777	6.682	40.236	1.00	20.06	7
ATOM	887	CD	PRO	397	11.042	6.990	38.829	1.00	19.90	6

ATOM	888	CA	PRO	397	11.166	5.309	40.578	1.00 21.55	6
ATOM	889	CB	PRO	397	11.424	4.652	39.217	1.00 23.55	6
ATOM	890	CG	PRO	397	11.842	5.775	38.372	1.00 24.21	6
ATOM	891	C	PRO	397	12.347	5.169	41.470	1.00 24.51	6
ATOM	892	O	PRO	397	12.550	4.095	42.008	1.00 26.01	8
ATOM	893	N	ASP	398	13.084	6.256	41.659	1.00 26.15	7
ATOM	894	CA	ASP	398	14.284	6.238	42.482	1.00 30.10	6
ATOM	895	CB	ASP	398	15.325	7.140	41.810	1.00 34.11	6
ATOM	896	CG	ASP	398	14.840	8.598	41.658	1.00 40.89	6
ATOM	897	OD1	ASP	398	15.380	9.452	42.392	1.00 45.30	8
ATOM	898	OD2	ASP	398	13.930	8.917	40.828	1.00 44.89	8
ATOM	899	C	ASP	398	14.054	6.620	43.958	1.00 28.78	6
ATOM	900	O	ASP	398	15.020	6.840	44.693	1.00 28.70	8
ATOM	901	N	ARG	399	12.797	6.683	44.399	1.00 26.20	7
ATOM	902	CA	ARG	399	12.540	7.026	45.788	1.00 27.04	6
ATOM	903	CB	ARG	399	11.029	7.259	46.052	1.00 26.80	6
ATOM	904	CG	ARG	399	10.362	8.314	45.160	1.00 25.69	6
ATOM	905	CD	ARG	399	11.016	9.589	45.506	1.00 26.81	6
ATOM	906	NE	ARG	399	10.400	10.788	45.016	1.00 26.65	7
ATOM	907	CZ	ARG	399	10.916	11.971	45.103	1.00 28.44	6
ATOM	908	NH1	ARG	399	12.075	12.047	45.724	1.00 34.16	7
ATOM	909	NH2	ARG	399	10.372	13.036	44.484	1.00 21.40	7
ATOM	910	C	ARG	399	13.065	5.975	46.764	1.00 29.93	6
ATOM	911	O	ARG	399	13.075	4.762	46.502	1.00 30.14	8
ATOM	912	N	GLN	400	13.483	6.453	47.921	1.00 30.34	7
ATOM	913	CA	GLN	400	13.987	5.555	48.924	1.00 32.89	6
ATOM	914	CB	GLN	400	14.485	6.364	50.121	1.00 36.60	6
ATOM	915	CG	GLN	400	15.498	5.625	50.996	1.00 43.09	6
ATOM	916	CD	GLN	400	16.776	6.462	51.193	1.00 46.68	6
ATOM	917	OE1	GLN	400	16.701	7.607	51.691	1.00 48.33	8
ATOM	918	NE2	GLN	400	17.954	5.907	50.783	1.00 48.29	7
ATOM	919	C	GLN	400	12.834	4.646	49.332	1.00 31.46	6
ATOM	920	O	GLN	400	11.666	5.050	49.256	1.00 31.23	8
ATOM	921	N	TYR	401	13.164	3.413	49.689	1.00 29.84	7
ATOM	922	CA	TYR	401	12.181	2.432	50.150	1.00 30.47	6
ATOM	923	CB	TYR	401	11.353	2.993	51.323	1.00 33.56	6
ATOM	924	CG	TYR	401	12.201	3.584	52.426	1.00 37.77	6
ATOM	925	CD1	TYR	401	13.073	2.786	53.193	1.00 40.82	6
ATOM	926	CE1	TYR	401	13.944	3.378	54.186	1.00 42.16	6
ATOM	927	CD2	TYR	401	12.192	4.956	52.654	1.00 40.80	6
ATOM	928	CE2	TYR	401	13.037	5.560	53.620	1.00 42.75	6
ATOM	929	CZ	TYR	401	13.910	4.779	54.386	1.00 42.98	6
ATOM	930	OH	TYR	401	14.686	5.467	55.325	1.00 43.71	8
ATOM	931	C	TYR	401	11.238	1.864	49.100	1.00 27.69	6
ATOM	932	O	TYR	401	10.370	1.092	49.459	1.00 30.16	8
ATOM	933	N	ILE	402	11.404	2.203	47.816	1.00 25.78	7
ATOM	934	CA	ILE	402	10.553	1.613	46.774	1.00 22.84	6
ATOM	935	CB	ILE	402	10.657	2.402	45.434	1.00 23.00	6
ATOM	936	CG2	ILE	402	9.958	1.650	44.282	1.00 20.56	6
ATOM	937	CG1	ILE	402	10.121	3.850	45.653	1.00 22.46	6
ATOM	938	CD1	ILE	402	8.640	3.961	46.085	1.00 19.57	6
ATOM	939	C	ILE	402	10.952	0.141	46.543	1.00 23.39	6
ATOM	940	O	ILE	402	12.110	-0.159	46.267	1.00 24.51	8
ATOM	941	N	LYS	403	10.012	-0.776	46.672	1.00 21.45	7
ATOM	942	CA	LYS	403	10.322	-2.199	46.454	1.00 22.37	6
ATOM	943	CB	LYS	403	9.377	-3.054	47.297	1.00 23.85	6
ATOM	944	CG	LYS	403	9.285	-2.666	48.755	1.00 24.84	6
ATOM	945	CD	LYS	403	8.266	-3.523	49.543	1.00 27.54	6

ATOM	946	CE	LYS	403	6.847	-3.362	48.990	1.00	29.42	6
ATOM	947	NZ	LYS	403	5.777	-4.144	49.737	1.00	26.53	7
ATOM	948	C	LYS	403	10.212	-2.600	44.958	1.00	21.56	6
ATOM	949	O	LYS	403	10.998	-3.437	44.464	1.00	23.77	8
ATOM	950	N	ASP	404	9.264	-2.031	44.218	1.00	19.81	7
ATOM	951	CA	ASP	404	9.109	-2.402	42.834	1.00	19.54	6
ATOM	952	CB	ASP	404	7.707	-2.981	42.650	1.00	20.40	6
ATOM	953	CG	ASP	404	7.491	-3.598	41.294	1.00	21.64	6
ATOM	954	OD1	ASP	404	8.262	-3.275	40.332	1.00	22.02	8
ATOM	955	OD2	ASP	404	6.537	-4.396	41.166	1.00	22.85	8
ATOM	956	C	ASP	404	9.316	-1.123	41.999	1.00	21.83	6
ATOM	957	O	ASP	404	8.330	-0.405	41.698	1.00	20.39	8
ATOM	958	N	ARG	405	10.620	-0.763	41.740	1.00	19.67	7
ATOM	959	CA	ARG	405	10.922	0.446	40.934	1.00	21.72	6
ATOM	960	CB	ARG	405	12.422	0.802	40.947	1.00	22.49	6
ATOM	961	CG	ARG	405	12.991	1.041	42.311	1.00	26.87	6
ATOM	962	CD	ARG	405	14.505	1.034	42.248	1.00	28.56	6
ATOM	963	NE	ARG	405	15.045	1.021	43.580	1.00	33.84	7
ATOM	964	CZ	ARG	405	14.837	1.983	44.449	1.00	35.85	6
ATOM	965	NH1	ARG	405	14.045	2.999	44.068	1.00	39.18	7
ATOM	966	NH2	ARG	405	15.510	1.994	45.616	1.00	33.69	7
ATOM	967	C	ARG	405	10.479	0.333	39.464	1.00	20.83	6
ATOM	968	O	ARG	405	10.122	1.370	38.840	1.00	20.11	8
ATOM	969	N	GLU	406	10.452	-0.902	38.830	1.00	18.43	7
ATOM	970	CA	GLU	406	10.075	-0.883	37.436	1.00	21.37	6
ATOM	971	CB	GLU	406	10.438	-2.201	36.709	1.00	27.61	6
ATOM	972	CG	GLU	406	9.622	-3.386	37.197	1.00	35.26	6
ATOM	973	CD	GLU	406	8.356	-3.661	36.318	1.00	43.68	6
ATOM	974	OE1	GLU	406	8.048	-2.857	35.350	1.00	46.60	8
ATOM	975	OE2	GLU	406	7.660	-4.693	36.586	1.00	47.06	8
ATOM	976	C	GLU	406	8.586	-0.573	37.256	1.00	20.47	6
ATOM	977	O	GLU	406	8.189	0.016	36.234	1.00	18.47	8
ATOM	978	N	ALA	407	7.755	-1.010	38.215	1.00	18.83	7
ATOM	979	CA	ALA	407	6.306	-0.704	38.153	1.00	18.20	6
ATOM	980	CB	ALA	407	5.581	-1.288	39.387	1.00	18.50	6
ATOM	981	C	ALA	407	6.170	0.845	38.153	1.00	17.66	6
ATOM	982	O	ALA	407	5.344	1.397	37.405	1.00	18.48	8
ATOM	983	N	VAL	408	6.968	1.577	38.954	1.00	17.76	7
ATOM	984	CA	VAL	408	6.823	3.087	38.926	1.00	18.35	6
ATOM	985	CB	VAL	408	7.570	3.805	40.157	1.00	18.47	6
ATOM	986	CG1	VAL	408	7.318	5.370	40.146	1.00	14.56	6
ATOM	987	CG2	VAL	408	7.098	3.190	41.478	1.00	15.70	6
ATOM	988	C	VAL	408	7.337	3.652	37.617	1.00	19.56	6
ATOM	989	O	VAL	408	6.735	4.546	36.974	1.00	19.62	8
ATOM	990	N	GLU	409	8.476	3.117	37.201	1.00	19.33	7
ATOM	991	CA	GLU	409	9.068	3.554	35.922	1.00	21.81	6
ATOM	992	CB	GLU	409	10.298	2.680	35.676	1.00	20.80	6
ATOM	993	CG	GLU	409	10.995	2.934	34.387	1.00	30.47	6
ATOM	994	CD	GLU	409	12.256	2.050	34.269	1.00	34.12	6
ATOM	995	OE1	GLU	409	12.110	0.809	34.458	1.00	35.74	8
ATOM	996	OE2	GLU	409	13.358	2.621	34.007	1.00	37.61	8
ATOM	997	C	GLU	409	8.039	3.425	34.774	1.00	19.31	6
ATOM	998	O	GLU	409	7.899	4.303	33.897	1.00	20.15	8
ATOM	999	N	LYS	410	7.301	2.324	34.775	1.00	20.62	7
ATOM	1000	CA	LYS	410	6.308	2.109	33.710	1.00	21.57	6
ATOM	1001	CB	LYS	410	5.782	0.684	33.794	1.00	22.00	6
ATOM	1002	CG	LYS	410	6.881	-0.318	33.434	1.00	24.82	6
ATOM	1003	CD	LYS	410	6.439	-1.772	33.607	1.00	29.47	6

ATOM	1004	CE	LYS	410	7.583	-2.728	33.207	1.00 31.74	6
ATOM	1005	NZ	LYS	410	7.101	-4.120	33.517	1.00 35.37	7
ATOM	1006	C	LYS	410	5.162	3.129	33.721	1.00 20.15	6
ATOM	1007	O	LYS	410	4.450	3.348	32.704	1.00 18.16	8
ATOM	1008	N	LEU	411	4.966	3.733	34.888	1.00 18.65	7
ATOM	1009	CA	LEU	411	3.936	4.742	35.048	1.00 17.75	6
ATOM	1010	CB	LEU	411	3.420	4.748	36.533	1.00 18.67	6
ATOM	1011	CG	LEU	411	2.598	3.520	36.922	1.00 20.48	6
ATOM	1012	CD1	LEU	411	1.931	3.757	38.334	1.00 20.57	6
ATOM	1013	CD2	LEU	411	1.473	3.352	35.836	1.00 20.41	6
ATOM	1014	C	LEU	411	4.522	6.088	34.705	1.00 16.78	6
ATOM	1015	O	LEU	411	3.864	6.948	34.158	1.00 18.66	8
ATOM	1016	N	GLN	412	5.798	6.282	35.015	1.00 16.32	7
ATOM	1017	CA	GLN	412	6.392	7.587	34.783	1.00 14.92	6
ATOM	1018	CB	GLN	412	7.670	7.742	35.625	1.00 15.65	6
ATOM	1019	CG	GLN	412	8.145	9.185	35.732	1.00 15.44	6
ATOM	1020	CD	GLN	412	9.539	9.267	36.263	1.00 16.45	6
ATOM	1021	OE1	GLN	412	10.436	8.556	35.781	1.00 15.48	8
ATOM	1022	NE2	GLN	412	9.759	10.128	37.256	1.00 12.68	7
ATOM	1023	C	GLN	412	6.764	7.849	33.312	1.00 17.36	6
ATOM	1024	O	GLN	412	6.637	8.940	32.821	1.00 15.53	8
ATOM	1025	N	GLU	413	7.096	6.939	32.586	1.00 18.73	7
ATOM	1026	CA	GLU	413	7.755	6.989	31.266	1.00 21.78	6
ATOM	1027	CB	GLU	413	8.276	5.588	30.880	1.00 24.70	6
ATOM	1028	CG	GLU	413	9.704	5.651	30.307	1.00 33.12	6
ATOM	1029	CD	GLU	413	10.727	6.545	31.138	1.00 37.10	6
ATOM	1030	OE1	GLU	413	11.030	6.266	32.325	1.00 37.65	8
ATOM	1031	OE2	GLU	413	11.247	7.547	30.575	1.00 39.21	8
ATOM	1032	C	GLU	413	6.855	7.573	30.142	1.00 19.47	6
ATOM	1033	O	GLU	413	7.291	8.385	29.351	1.00 18.65	8
ATOM	1034	N	PRO	414	5.459	7.146	30.378	1.00 20.07	7
ATOM	1035	CD	PRO	414	5.067	5.893	31.055	1.00 19.68	6
ATOM	1036	CA	PRO	414	4.401	7.717	29.518	1.00 19.49	6
ATOM	1037	CB	PRO	414	3.137	6.902	29.854	1.00 19.44	6
ATOM	1038	CG	PRO	414	3.677	5.575	30.456	1.00 23.13	6
ATOM	1039	C	PRO	414	4.172	9.222	29.800	1.00 19.10	6
ATOM	1040	O	PRO	414	3.825	9.991	28.910	1.00 16.88	8
ATOM	1041	N	LEU	415	4.340	9.636	31.050	1.00 17.87	7
ATOM	1042	CA	LEU	415	4.102	11.070	31.395	1.00 17.08	6
ATOM	1043	CB	LEU	415	3.944	11.215	32.935	1.00 18.37	6
ATOM	1044	CG	LEU	415	2.775	10.339	33.494	1.00 18.91	6
ATOM	1045	CD1	LEU	415	2.575	10.455	34.992	1.00 18.35	6
ATOM	1046	CD2	LEU	415	1.472	10.791	32.774	1.00 21.95	6
ATOM	1047	C	LEU	415	5.256	11.903	30.877	1.00 16.87	6
ATOM	1048	O	LEU	415	5.088	13.033	30.418	1.00 15.92	8
ATOM	1049	N	LEU	416	6.455	11.346	30.994	1.00 16.05	7
ATOM	1050	CA	LEU	416	7.605	12.040	30.455	1.00 16.12	6
ATOM	1051	CB	LEU	416	8.857	11.237	30.725	1.00 14.67	6
ATOM	1052	CG	LEU	416	9.381	11.348	32.170	1.00 15.86	6
ATOM	1053	CD1	LEU	416	10.281	10.101	32.507	1.00 17.06	6
ATOM	1054	CD2	LEU	416	10.129	12.651	32.292	1.00 17.58	6
ATOM	1055	C	LEU	416	7.410	12.210	28.921	1.00 15.67	6
ATOM	1056	O	LEU	416	7.773	13.255	28.359	1.00 16.65	8
ATOM	1057	N	ASP	417	6.901	11.178	28.245	1.00 17.40	7
ATOM	1058	CA	ASP	417	6.636	11.302	26.808	1.00 18.62	6
ATOM	1059	CB	ASP	417	6.176	9.941	26.211	1.00 20.86	6
ATOM	1060	CG	ASP	417	7.320	8.885	26.214	1.00 23.35	6
ATOM	1061	OD1	ASP	417	8.466	9.315	26.294	1.00 24.26	8

ATOM	1062	OD2	ASP	417	7.096	7.651	26.102	1.00	24.28	8
ATOM	1063	C	ASP	417	5.591	12.425	26.532	1.00	18.79	6
ATOM	1064	O	ASP	417	5.782	13.213	25.589	1.00	20.06	8
ATOM	1065	N	VAL	418	4.483	12.473	27.289	1.00	16.50	7
ATOM	1066	CA	VAL	418	3.523	13.552	27.119	1.00	16.29	6
ATOM	1067	CB	VAL	418	2.276	13.369	28.019	1.00	18.28	6
ATOM	1068	CG1	VAL	418	1.410	14.652	27.991	1.00	16.09	6
ATOM	1069	CG2	VAL	418	1.462	12.108	27.519	1.00	17.51	6
ATOM	1070	C	VAL	418	4.154	14.935	27.402	1.00	18.27	6
ATOM	1071	O	VAL	418	3.923	15.901	26.637	1.00	18.89	8
ATOM	1072	N	LEU	419	5.006	15.032	28.427	1.00	16.19	7
ATOM	1073	CA	LEU	419	5.625	16.328	28.730	1.00	16.99	6
ATOM	1074	CB	LEU	419	6.393	16.262	30.058	1.00	14.52	6
ATOM	1075	CG	LEU	419	7.078	17.571	30.398	1.00	17.89	6
ATOM	1076	CD1	LEU	419	5.986	18.713	30.571	1.00	16.23	6
ATOM	1077	CD2	LEU	419	7.931	17.304	31.746	1.00	16.46	6
ATOM	1078	C	LEU	419	6.547	16.760	27.607	1.00	17.42	6
ATOM	1079	O	LEU	419	6.566	17.949	27.191	1.00	14.69	8
ATOM	1080	N	GLN	420	7.321	15.824	27.102	1.00	19.78	7
ATOM	1081	CA	GLN	420	8.196	16.194	25.978	1.00	22.39	6
ATOM	1082	CB	GLN	420	9.019	14.996	25.554	1.00	26.26	6
ATOM	1083	CG	GLN	420	9.848	15.238	24.317	1.00	31.05	6
ATOM	1084	CD	GLN	420	10.542	13.952	23.893	1.00	36.40	6
ATOM	1085	OE1	GLN	420	11.542	13.563	24.497	1.00	37.49	8
ATOM	1086	NE2	GLN	420	9.993	13.271	22.859	1.00	38.17	7
ATOM	1087	C	GLN	420	7.325	16.719	24.799	1.00	23.07	6
ATOM	1088	O	GLN	420	7.654	17.739	24.141	1.00	24.67	8
ATOM	1089	N	LYS	421	6.238	16.044	24.465	1.00	21.61	7
ATOM	1090	CA	LYS	421	5.366	16.635	23.452	1.00	22.20	6
ATOM	1091	CB	LYS	421	4.127	15.767	23.208	1.00	23.43	6
ATOM	1092	CG	LYS	421	4.413	14.373	22.783	1.00	29.40	6
ATOM	1093	CD	LYS	421	5.095	14.348	21.485	1.00	32.52	6
ATOM	1094	CE	LYS	421	5.072	12.897	20.824	1.00	36.37	6
ATOM	1095	NZ	LYS	421	3.653	12.299	20.674	1.00	37.16	7
ATOM	1096	C	LYS	421	4.805	18.045	23.841	1.00	20.49	6
ATOM	1097	O	LYS	421	4.708	18.927	22.985	1.00	20.84	8
ATOM	1098	N	LEU	422	4.389	18.247	25.098	1.00	19.58	7
ATOM	1099	CA	LEU	422	3.824	19.540	25.517	1.00	18.69	6
ATOM	1100	CB	LEU	422	3.382	19.511	26.966	1.00	17.35	6
ATOM	1101	CG	LEU	422	2.127	18.675	27.223	1.00	19.81	6
ATOM	1102	CD1	LEU	422	1.821	18.558	28.701	1.00	21.65	6
ATOM	1103	CD2	LEU	422	0.995	19.354	26.437	1.00	22.49	6
ATOM	1104	C	LEU	422	4.843	20.640	25.328	1.00	20.29	6
ATOM	1105	O	LEU	422	4.479	21.751	24.894	1.00	19.74	8
ATOM	1106	N	CYS	423	6.106	20.331	25.643	1.00	18.79	7
ATOM	1107	CA	CYS	423	7.190	21.322	25.464	1.00	20.73	6
ATOM	1108	CB	CYS	423	8.541	20.707	25.915	1.00	18.78	6
ATOM	1109	SG	CYS	423	8.497	20.555	27.781	1.00	19.20	16
ATOM	1110	C	CYS	423	7.278	21.751	23.982	1.00	22.59	6
ATOM	1111	O	CYS	423	7.554	22.908	23.683	1.00	22.67	8
ATOM	1112	N	LYS	424	7.068	20.837	23.075	1.00	23.92	7
ATOM	1113	CA	LYS	424	7.221	21.223	21.673	1.00	26.49	6
ATOM	1114	CB	LYS	424	7.472	19.955	20.851	1.00	30.34	6
ATOM	1115	CG	LYS	424	7.305	20.100	19.372	1.00	37.67	6
ATOM	1116	CD	LYS	424	8.387	19.326	18.699	1.00	42.21	6
ATOM	1117	CE	LYS	424	8.253	19.450	17.190	1.00	44.24	6
ATOM	1118	NZ	LYS	424	6.786	19.345	16.808	1.00	47.45	7
ATOM	1119	C	LYS	424	5.930	21.935	21.184	1.00	27.23	6

ATOM	1120	O	LYS	424	6.006	22.934	20.480	1.00	28.14	8
ATOM	1121	N	ILE	425	4.703	21.559	21.818	1.00	26.63	7
ATOM	1122	CA	ILE	425	3.442	22.266	21.508	1.00	27.00	6
ATOM	1123	CB	ILE	425	2.169	21.530	22.153	1.00	27.35	6
ATOM	1124	CG2	ILE	425	0.868	22.531	22.190	1.00	27.37	6
ATOM	1125	CG1	ILE	425	1.902	20.214	21.397	1.00	28.64	6
ATOM	1126	CD1	ILE	425	0.812	19.385	22.076	1.00	31.67	6
ATOM	1127	C	ILE	425	3.446	23.735	22.008	1.00	26.48	6
ATOM	1128	O	ILE	425	3.099	24.670	21.279	1.00	26.48	8
ATOM	1129	N	HIS	426	3.854	23.939	23.249	1.00	24.95	7
ATOM	1130	CA	HIS	426	3.835	25.271	23.794	1.00	24.86	6
ATOM	1131	CB	HIS	426	3.556	25.183	25.313	1.00	24.69	6
ATOM	1132	CG	HIS	426	2.162	24.729	25.641	1.00	24.71	6
ATOM	1133	CD2	HIS	426	0.954	25.213	25.250	1.00	23.92	6
ATOM	1134	ND1	HIS	426	1.900	23.613	26.415	1.00	22.78	7
ATOM	1135	CE1	HIS	426	0.588	23.422	26.479	1.00	22.53	6
ATOM	1136	NE2	HIS	426	-0.006	24.379	25.772	1.00	25.71	7
ATOM	1137	C	HIS	426	5.067	26.181	23.514	1.00	24.55	6
ATOM	1138	O	HIS	426	4.975	27.391	23.632	1.00	22.28	8
ATOM	1139	N	GLN	427	6.204	25.609	23.167	1.00	24.11	7
ATOM	1140	CA	GLN	427	7.384	26.419	22.917	1.00	25.32	6
ATOM	1141	CB	GLN	427	8.242	26.553	24.192	1.00	26.75	6
ATOM	1142	CG	GLN	427	7.637	27.413	25.340	1.00	26.51	6
ATOM	1143	CD	GLN	427	8.673	27.750	26.439	1.00	31.10	6
ATOM	1144	OE1	GLN	427	8.298	28.044	27.603	1.00	31.48	8
ATOM	1145	NE2	GLN	427	9.983	27.723	26.074	1.00	29.86	7
ATOM	1146	C	GLN	427	8.176	25.801	21.774	1.00	27.56	6
ATOM	1147	O	GLN	427	9.351	25.445	21.898	1.00	27.06	8
ATOM	1148	N	PRO	428	7.526	25.701	20.611	1.00	28.74	7
ATOM	1149	CD	PRO	428	6.245	26.324	20.249	1.00	28.48	6
ATOM	1150	CA	PRO	428	8.180	25.117	19.442	1.00	30.35	6
ATOM	1151	CB	PRO	428	7.117	25.238	18.356	1.00	31.91	6
ATOM	1152	CG	PRO	428	6.382	26.508	18.729	1.00	30.42	6
ATOM	1153	C	PRO	428	9.479	25.810	19.038	1.00	31.95	6
ATOM	1154	O	PRO	428	10.299	25.186	18.399	1.00	32.66	8
ATOM	1155	N	GLU	429	9.667	27.069	19.425	1.00	33.51	7
ATOM	1156	CA	GLU	429	10.859	27.813	19.022	1.00	36.19	6
ATOM	1157	CB	GLU	429	10.551	29.310	18.872	1.00	36.14	6
ATOM	1158	CG	GLU	429	10.297	30.096	20.176	1.00	39.46	6
ATOM	1159	CD	GLU	429	9.103	29.596	21.022	1.00	41.32	6
ATOM	1160	OE1	GLU	429	7.989	29.298	20.502	1.00	41.17	8
ATOM	1161	OE2	GLU	429	9.300	29.540	22.247	1.00	43.92	8
ATOM	1162	C	GLU	429	12.013	27.634	19.977	1.00	37.32	6
ATOM	1163	O	GLU	429	13.050	28.270	19.799	1.00	39.02	8
ATOM	1164	N	ASN	430	11.836	26.761	20.970	1.00	36.99	7
ATOM	1165	CA	ASN	430	12.834	26.506	21.996	1.00	37.06	6
ATOM	1166	CB	ASN	430	12.363	27.170	23.307	1.00	41.16	6
ATOM	1167	CG	ASN	430	13.477	27.336	24.337	1.00	44.13	6
ATOM	1168	OD1	ASN	430	13.537	28.359	25.036	1.00	47.94	8
ATOM	1169	ND2	ASN	430	14.361	26.343	24.441	1.00	46.05	7
ATOM	1170	C	ASN	430	12.987	24.993	22.160	1.00	36.64	6
ATOM	1171	O	ASN	430	12.451	24.396	23.099	1.00	33.95	8
ATOM	1172	N	PRO	431	13.740	24.352	21.243	1.00	35.67	7
ATOM	1173	CD	PRO	431	14.370	24.993	20.073	1.00	35.91	6
ATOM	1174	CA	PRO	431	13.986	22.904	21.234	1.00	35.65	6
ATOM	1175	CB	PRO	431	14.861	22.705	20.011	1.00	36.93	6
ATOM	1176	CG	PRO	431	14.439	23.852	19.098	1.00	36.97	6
ATOM	1177	C	PRO	431	14.618	22.263	22.475	1.00	35.36	6

ATOM	1178	O	PRO	431	14.462	21.068	22.708	1.00 35.99	8
ATOM	1179	N	GLN	432	15.339	23.055	23.260	1.00 33.39	7
ATOM	1180	CA	GLN	432	15.956	22.543	24.458	1.00 31.54	6
ATOM	1181	CB	GLN	432	17.223	23.354	24.773	1.00 35.01	6
ATOM	1182	CG	GLN	432	16.953	24.594	25.632	1.00 40.15	6
ATOM	1183	CD	GLN	432	17.928	25.747	25.322	1.00 43.73	6
ATOM	1184	OE1	GLN	432	18.073	26.139	24.153	1.00 46.27	8
ATOM	1185	NE2	GLN	432	18.607	26.284	26.365	1.00 44.57	7
ATOM	1186	C	GLN	432	15.002	22.700	25.643	1.00 28.52	6
ATOM	1187	O	GLN	432	15.365	22.363	26.758	1.00 26.75	8
ATOM	1188	N	HIS	433	13.804	23.229	25.412	1.00 24.03	7
ATOM	1189	CA	HIS	433	12.917	23.476	26.549	1.00 22.84	6
ATOM	1190	CB	HIS	433	11.577	24.050	26.043	1.00 22.27	6
ATOM	1191	CG	HIS	433	10.614	24.385	27.140	1.00 23.73	6
ATOM	1192	CD2	HIS	433	9.322	24.023	27.333	1.00 22.94	6
ATOM	1193	ND1	HIS	433	10.904	25.303	28.125	1.00 22.94	7
ATOM	1194	CE1	HIS	433	9.827	25.517	28.861	1.00 23.55	6
ATOM	1195	NE2	HIS	433	8.852	24.748	28.402	1.00 24.36	7
ATOM	1196	C	HIS	433	12.693	22.270	27.479	1.00 21.51	6
ATOM	1197	O	HIS	433	12.811	22.383	28.725	1.00 22.71	8
ATOM	1198	N	PHE	434	12.465	21.103	26.886	1.00 20.30	7
ATOM	1199	CA	PHE	434	12.183	19.915	27.679	1.00 24.11	6
ATOM	1200	CB	PHE	434	11.810	18.725	26.813	1.00 24.68	6
ATOM	1201	CG	PHE	434	11.644	17.432	27.598	1.00 26.29	6
ATOM	1202	CD1	PHE	434	10.509	17.272	28.404	1.00 26.38	6
ATOM	1203	CD2	PHE	434	12.534	16.334	27.433	1.00 26.46	6
ATOM	1204	CE1	PHE	434	10.231	16.066	29.010	1.00 26.26	6
ATOM	1205	CE2	PHE	434	12.274	15.081	28.049	1.00 26.51	6
ATOM	1206	CZ	PHE	434	11.100	14.954	28.841	1.00 26.11	6
ATOM	1207	C	PHE	434	13.366	19.581	28.564	1.00 25.13	6
ATOM	1208	O	PHE	434	13.191	19.238	29.768	1.00 23.78	8
ATOM	1209	N	ALA	435	14.564	19.681	27.979	1.00 24.03	7
ATOM	1210	CA	ALA	435	15.801	19.471	28.753	1.00 25.07	6
ATOM	1211	CB	ALA	435	17.042	19.659	27.860	1.00 24.83	6
ATOM	1212	C	ALA	435	15.899	20.469	29.905	1.00 24.15	6
ATOM	1213	O	ALA	435	16.343	20.095	30.995	1.00 25.10	8
ATOM	1214	N	CYS	436	15.497	21.731	29.681	1.00 24.44	7
ATOM	1215	CA	CYS	436	15.579	22.766	30.729	1.00 26.19	6
ATOM	1216	CB	CYS	436	15.221	24.170	30.226	1.00 27.98	6
ATOM	1217	SG	CYS	436	16.405	24.731	28.990	1.00 36.71	16
ATOM	1218	C	CYS	436	14.688	22.425	31.889	1.00 25.04	6
ATOM	1219	O	CYS	436	15.084	22.641	33.029	1.00 25.74	8
ATOM	1220	N	LEU	437	13.515	21.857	31.603	1.00 23.61	7
ATOM	1221	CA	LEU	437	12.588	21.446	32.653	1.00 21.74	6
ATOM	1222	CB	LEU	437	11.277	20.892	32.094	1.00 23.21	6
ATOM	1223	CG	LEU	437	10.184	21.913	31.743	1.00 25.15	6
ATOM	1224	CD1	LEU	437	9.887	22.604	32.990	1.00 25.88	6
ATOM	1225	CD2	LEU	437	10.581	22.995	30.737	1.00 26.62	6
ATOM	1226	C	LEU	437	13.249	20.354	33.487	1.00 22.31	6
ATOM	1227	O	LEU	437	13.266	20.454	34.724	1.00 21.51	8
ATOM	1228	N	LEU	438	13.771	19.317	32.831	1.00 21.09	7
ATOM	1229	CA	LEU	438	14.422	18.247	33.572	1.00 25.04	6
ATOM	1230	CB	LEU	438	14.989	17.158	32.633	1.00 27.63	6
ATOM	1231	CG	LEU	438	13.897	16.509	31.808	1.00 28.85	6
ATOM	1232	CD1	LEU	438	14.464	15.409	30.940	1.00 29.12	6
ATOM	1233	CD2	LEU	438	12.828	15.983	32.761	1.00 28.90	6
ATOM	1234	C	LEU	438	15.551	18.814	34.428	1.00 25.06	6
ATOM	1235	O	LEU	438	15.723	18.420	35.583	1.00 24.77	8

ATOM	1236	N	GLY	439	16.281	19.773	33.860	1.00 27.05	7
ATOM	1237	CA	GLY	439	17.394	20.406	34.550	1.00 28.73	6
ATOM	1238	C	GLY	439	16.938	20.998	35.871	1.00 29.15	6
ATOM	1239	O	GLY	439	17.542	20.768	36.947	1.00 31.44	8
ATOM	1240	N	ARG	440	15.833	21.715	35.819	1.00 28.15	7
ATOM	1241	CA	ARG	440	15.292	22.355	37.016	1.00 28.50	6
ATOM	1242	CB	ARG	440	14.109	23.270	36.712	1.00 28.90	6
ATOM	1243	CG	ARG	440	14.430	24.413	35.749	1.00 32.17	6
ATOM	1244	CD	ARG	440	15.666	25.248	36.114	1.00 31.21	6
ATOM	1245	NE	ARG	440	15.609	26.637	35.634	1.00 32.35	7
ATOM	1246	CZ	ARG	440	16.008	27.102	34.438	1.00 32.55	6
ATOM	1247	NH1	ARG	440	16.534	26.276	33.522	1.00 28.84	7
ATOM	1248	NH2	ARG	440	15.872	28.411	34.158	1.00 30.85	7
ATOM	1249	C	ARG	440	14.911	21.367	38.093	1.00 29.85	6
ATOM	1250	O	ARG	440	14.803	21.758	39.267	1.00 26.84	8
ATOM	1251	N	LEU	441	14.699	20.097	37.711	1.00 29.24	7
ATOM	1252	CA	LEU	441	14.375	19.045	38.679	1.00 31.53	6
ATOM	1253	CB	LEU	441	14.062	17.743	37.945	1.00 32.72	6
ATOM	1254	CG	LEU	441	12.623	17.286	38.032	1.00 34.18	6
ATOM	1255	CD1	LEU	441	11.642	18.400	37.664	1.00 35.57	6
ATOM	1256	CD2	LEU	441	12.460	16.117	37.106	1.00 35.32	6
ATOM	1257	C	LEU	441	15.511	18.838	39.689	1.00 30.69	6
ATOM	1258	O	LEU	441	15.269	18.523	40.877	1.00 31.86	8
ATOM	1259	N	THR	442	16.749	19.015	39.231	1.00 30.05	7
ATOM	1260	CA	THR	442	17.906	18.910	40.105	1.00 29.81	6
ATOM	1261	CB	THR	442	19.273	19.045	39.309	1.00 31.61	6
ATOM	1262	OG1	THR	442	19.473	17.870	38.508	1.00 35.27	8
ATOM	1263	CG2	THR	442	20.396	19.124	40.217	1.00 30.46	6
ATOM	1264	C	THR	442	17.857	19.999	41.193	1.00 28.42	6
ATOM	1265	O	THR	442	18.097	19.713	42.385	1.00 26.82	8
ATOM	1266	N	GLU	443	17.545	21.232	40.786	1.00 24.22	7
ATOM	1267	CA	GLU	443	17.446	22.325	41.724	1.00 22.79	6
ATOM	1268	CB	GLU	443	17.148	23.638	40.973	1.00 24.26	6
ATOM	1269	CG	GLU	443	17.134	24.841	41.903	1.00 27.14	6
ATOM	1270	CD	GLU	443	16.927	26.171	41.174	1.00 31.11	6
ATOM	1271	OE1	GLU	443	16.882	27.217	41.855	1.00 31.94	8
ATOM	1272	OE2	GLU	443	16.798	26.174	39.915	1.00 32.42	8
ATOM	1273	C	GLU	443	16.313	22.011	42.705	1.00 21.04	6
ATOM	1274	O	GLU	443	16.373	22.277	43.913	1.00 20.94	8
ATOM	1275	N	LEU	444	15.253	21.438	42.187	1.00 19.67	7
ATOM	1276	CA	LEU	444	14.107	21.143	43.057	1.00 19.40	6
ATOM	1277	CB	LEU	444	12.935	20.613	42.237	1.00 19.41	6
ATOM	1278	CG	LEU	444	11.636	20.330	42.996	1.00 19.58	6
ATOM	1279	CD1	LEU	444	11.066	21.637	43.571	1.00 16.04	6
ATOM	1280	CD2	LEU	444	10.714	19.622	42.043	1.00 21.69	6
ATOM	1281	C	LEU	444	14.451	20.131	44.166	1.00 19.39	6
ATOM	1282	O	LEU	444	13.982	20.243	45.313	1.00 15.57	8
ATOM	1283	N	ARG	445	15.298	19.165	43.837	1.00 18.73	7
ATOM	1284	CA	ARG	445	15.602	18.165	44.832	1.00 18.88	6
ATOM	1285	CB	ARG	445	16.237	16.927	44.221	1.00 23.88	6
ATOM	1286	CG	ARG	445	15.353	16.194	43.227	1.00 28.79	6
ATOM	1287	CD	ARG	445	16.028	14.912	42.748	1.00 34.64	6
ATOM	1288	NE	ARG	445	15.352	14.341	41.565	1.00 38.63	7
ATOM	1289	CZ	ARG	445	15.643	14.622	40.286	1.00 40.01	6
ATOM	1290	NH1	ARG	445	16.616	15.464	39.978	1.00 41.00	7
ATOM	1291	NH2	ARG	445	14.935	14.074	39.297	1.00 41.02	7
ATOM	1292	C	ARG	445	16.462	18.675	45.950	1.00 18.83	6
ATOM	1293	O	ARG	445	16.517	18.039	47.006	1.00 18.30	8

ATOM	1294	N	THR	446	17.155	19.787	45.744	1.00 18.21	7
ATOM	1295	CA	THR	446	17.960	20.307	46.858	1.00 20.13	6
ATOM	1296	CB	THR	446	18.844	21.558	46.456	1.00 18.59	6
ATOM	1297	OG1	THR	446	18.003	22.682	46.254	1.00 19.19	8
ATOM	1298	CG2	THR	446	19.700	21.300	45.145	1.00 19.27	6
ATOM	1299	C	THR	446	17.050	20.707	48.039	1.00 20.34	6
ATOM	1300	O	THR	446	17.500	20.751	49.212	1.00 21.59	8
ATOM	1301	N	PHE	447	15.777	21.045	47.767	1.00 18.53	7
ATOM	1302	CA	PHE	447	14.915	21.416	48.882	1.00 16.86	6
ATOM	1303	CB	PHE	447	13.594	22.017	48.402	1.00 18.21	6
ATOM	1304	CG	PHE	447	13.800	23.366	47.776	1.00 19.49	6
ATOM	1305	CD1	PHE	447	14.001	23.484	46.399	1.00 17.01	6
ATOM	1306	CD2	PHE	447	13.979	24.498	48.590	1.00 18.47	6
ATOM	1307	CE1	PHE	447	14.391	24.734	45.824	1.00 18.27	6
ATOM	1308	CE2	PHE	447	14.368	25.727	48.019	1.00 17.72	6
ATOM	1309	CZ	PHE	447	14.569	25.824	46.636	1.00 16.62	6
ATOM	1310	C	PHE	447	14.680	20.288	49.840	1.00 15.58	6
ATOM	1311	O	PHE	447	14.257	20.551	50.968	1.00 15.13	8
ATOM	1312	N	ASN	448	14.953	19.048	49.443	1.00 14.96	7
ATOM	1313	CA	ASN	448	14.792	17.956	50.442	1.00 15.50	6
ATOM	1314	CB	ASN	448	15.042	16.598	49.822	1.00 15.33	6
ATOM	1315	CG	ASN	448	13.972	16.209	48.904	1.00 18.64	6
ATOM	1316	OD1	ASN	448	12.776	16.155	49.265	1.00 19.32	8
ATOM	1317	ND2	ASN	448	14.371	15.940	47.675	1.00 15.83	7
ATOM	1318	C	ASN	448	15.789	18.185	51.633	1.00 16.62	6
ATOM	1319	O	ASN	448	15.496	17.928	52.821	1.00 15.09	8
ATOM	1320	N	HIS	449	16.965	18.719	51.294	1.00 17.00	7
ATOM	1321	CA	HIS	449	17.957	19.036	52.311	1.00 17.97	6
ATOM	1322	CB	HIS	449	19.346	19.023	51.676	1.00 21.40	6
ATOM	1323	CG	HIS	449	19.663	17.689	51.135	1.00 23.56	6
ATOM	1324	CD2	HIS	449	19.720	17.225	49.863	1.00 26.68	6
ATOM	1325	ND1	HIS	449	19.859	16.603	51.959	1.00 25.22	7
ATOM	1326	CE1	HIS	449	20.023	15.516	51.217	1.00 27.79	6
ATOM	1327	NE2	HIS	449	19.940	15.862	49.938	1.00 26.22	7
ATOM	1328	C	HIS	449	17.658	20.339	52.986	1.00 18.56	6
ATOM	1329	O	HIS	449	17.682	20.383	54.229	1.00 16.38	8
ATOM	1330	N	HIS	450	17.310	21.388	52.221	1.00 16.59	7
ATOM	1331	CA	HIS	450	17.028	22.660	52.870	1.00 17.63	6
ATOM	1332	CB	HIS	450	16.665	23.780	51.882	1.00 21.71	6
ATOM	1333	CG	HIS	450	17.696	24.036	50.837	1.00 25.68	6
ATOM	1334	CD2	HIS	450	17.596	24.064	49.477	1.00 26.30	6
ATOM	1335	ND1	HIS	450	19.017	24.310	51.142	1.00 26.33	7
ATOM	1336	CE1	HIS	450	19.684	24.503	50.007	1.00 29.65	6
ATOM	1337	NE2	HIS	450	18.848	24.361	48.984	1.00 27.96	7
ATOM	1338	C	HIS	450	15.873	22.515	53.867	1.00 16.73	6
ATOM	1339	O	HIS	450	15.905	23.121	54.957	1.00 15.77	8
ATOM	1340	N	HIS	451	14.880	21.712	53.515	1.00 14.42	7
ATOM	1341	CA	HIS	451	13.727	21.563	54.401	1.00 16.33	6
ATOM	1342	CB	HIS	451	12.643	20.849	53.647	1.00 17.84	6
ATOM	1343	CG	HIS	451	11.285	21.019	54.240	1.00 20.31	6
ATOM	1344	CD2	HIS	451	10.551	20.179	55.006	1.00 20.24	6
ATOM	1345	ND1	HIS	451	10.548	22.183	54.113	1.00 20.16	7
ATOM	1346	CE1	HIS	451	9.414	22.041	54.783	1.00 21.85	6
ATOM	1347	NE2	HIS	451	9.393	20.836	55.337	1.00 20.59	7
ATOM	1348	C	HIS	451	14.075	20.789	55.715	1.00 16.77	6
ATOM	1349	O	HIS	451	13.641	21.167	56.795	1.00 16.58	8
ATOM	1350	N	ALA	452	14.827	19.687	55.597	1.00 17.79	7
ATOM	1351	CA	ALA	452	15.230	18.880	56.784	1.00 20.08	6

ATOM	1352	CB	ALA	452	16.147	17.677	56.353	1.00 18.72	6
ATOM	1353	C	ALA	452	16.008	19.803	57.744	1.00 19.33	6
ATOM	1354	O	ALA	452	15.834	19.703	58.957	1.00 20.31	8
ATOM	1355	N	GLU	453	16.894	20.649	57.185	1.00 19.86	7
ATOM	1356	CA	GLU	453	17.723	21.603	57.977	1.00 19.53	6
ATOM	1357	CB	GLU	453	18.696	22.401	57.070	1.00 19.40	6
ATOM	1358	CG	GLU	453	19.665	23.329	57.876	1.00 24.14	6
ATOM	1359	CD	GLU	453	20.651	24.041	56.958	1.00 28.20	6
ATOM	1360	OE1	GLU	453	21.298	25.016	57.376	1.00 31.33	8
ATOM	1361	OE2	GLU	453	20.782	23.645	55.786	1.00 31.30	8
ATOM	1362	C	GLU	453	16.814	22.609	58.719	1.00 19.65	6
ATOM	1363	O	GLU	453	16.887	22.805	59.945	1.00 17.80	8
ATOM	1364	N	MET	454	15.953	23.228	57.928	1.00 17.19	7
ATOM	1365	CA	MET	454	15.022	24.199	58.417	1.00 18.01	6
ATOM	1366	CB	MET	454	14.175	24.689	57.230	1.00 18.26	6
ATOM	1367	CG	MET	454	13.148	25.715	57.594	1.00 18.57	6
ATOM	1368	SD	MET	454	11.605	25.022	58.285	1.00 19.34	16
ATOM	1369	CE	MET	454	10.805	24.045	56.759	1.00 17.75	6
ATOM	1370	C	MET	454	14.111	23.661	59.524	1.00 16.12	6
ATOM	1371	O	MET	454	13.902	24.335	60.530	1.00 16.56	8
ATOM	1372	N	LEU	455	13.573	22.468	59.350	1.00 15.99	7
ATOM	1373	CA	LEU	455	12.697	21.907	60.356	1.00 17.79	6
ATOM	1374	CB	LEU	455	12.143	20.592	59.832	1.00 19.10	6
ATOM	1375	CG	LEU	455	10.666	20.430	59.407	1.00 23.57	6
ATOM	1376	CD1	LEU	455	10.063	21.690	59.023	1.00 23.89	6
ATOM	1377	CD2	LEU	455	10.511	19.333	58.364	1.00 22.65	6
ATOM	1378	C	LEU	455	13.339	21.647	61.724	1.00 20.79	6
ATOM	1379	O	LEU	455	12.653	21.708	62.774	1.00 17.76	8
ATOM	1380	N	MET	456	14.648	21.353	61.693	1.00 18.90	7
ATOM	1381	CA	MET	456	15.344	20.946	62.892	1.00 21.58	6
ATOM	1382	CB	MET	456	16.840	20.677	62.600	1.00 23.24	6
ATOM	1383	CG	MET	456	17.436	19.752	63.648	1.00 31.39	6
ATOM	1384	SD	MET	456	16.527	18.145	63.770	1.00 37.13	16
ATOM	1385	CE	MET	456	16.639	17.762	61.998	1.00 30.52	6
ATOM	1386	C	MET	456	15.149	21.868	64.076	1.00 19.80	6
ATOM	1387	O	MET	456	14.804	21.383	65.151	1.00 21.15	8
ATOM	1388	N	SER	457	15.285	23.173	63.865	1.00 18.39	7
ATOM	1389	CA	SER	457	15.111	24.150	64.944	1.00 19.75	6
ATOM	1390	CB	SER	457	15.454	25.558	64.421	1.00 22.04	6
ATOM	1391	OG	SER	457	14.885	26.503	65.289	1.00 25.45	8
ATOM	1392	C	SER	457	13.692	24.124	65.569	1.00 18.21	6
ATOM	1393	O	SER	457	13.534	24.171	66.797	1.00 16.38	8
ATOM	1394	N	TRP	458	12.668	24.041	64.710	1.00 18.00	7
ATOM	1395	CA	TRP	458	11.287	23.922	65.146	1.00 18.11	6
ATOM	1396	CB	TRP	458	10.338	23.874	63.914	1.00 17.42	6
ATOM	1397	CG	TRP	458	10.376	25.142	63.132	1.00 19.25	6
ATOM	1398	CD2	TRP	458	9.632	26.364	63.422	1.00 20.22	6
ATOM	1399	CE2	TRP	458	9.987	27.318	62.403	1.00 20.22	6
ATOM	1400	CE3	TRP	458	8.715	26.740	64.422	1.00 21.29	6
ATOM	1401	CD1	TRP	458	11.138	25.408	62.010	1.00 23.66	6
ATOM	1402	NE1	TRP	458	10.897	26.726	61.573	1.00 22.29	7
ATOM	1403	CZ2	TRP	458	9.438	28.657	62.398	1.00 20.39	6
ATOM	1404	CZ3	TRP	458	8.172	28.067	64.412	1.00 20.96	6
ATOM	1405	CH2	TRP	458	8.536	29.000	63.406	1.00 19.89	6
ATOM	1406	C	TRP	458	11.142	22.593	65.923	1.00 17.70	6
ATOM	1407	O	TRP	458	10.426	22.540	66.885	1.00 17.69	8
ATOM	1408	N	ARG	459	11.814	21.522	65.505	1.00 15.90	7
ATOM	1409	CA	ARG	459	11.660	20.252	66.226	1.00 19.67	6

ATOM	1410	CB	ARG	459	12.283	19.058	65.471	1.00 17.13	6
ATOM	1411	CG	ARG	459	11.674	18.795	64.064	1.00 22.30	6
ATOM	1412	CD	ARG	459	12.080	17.424	63.441	1.00 27.44	6
ATOM	1413	NE	ARG	459	11.747	16.467	64.475	1.00 33.39	7
ATOM	1414	CZ	ARG	459	12.149	15.205	64.525	1.00 35.52	6
ATOM	1415	NH1	ARG	459	12.892	14.798	63.541	1.00 34.15	7
ATOM	1416	NH2	ARG	459	11.814	14.392	65.571	1.00 36.79	7
ATOM	1417	C	ARG	459	12.313	20.323	67.626	1.00 20.39	6
ATOM	1418	O	ARG	459	11.716	19.861	68.644	1.00 20.44	8
ATOM	1419	N	VAL	460	13.512	20.885	67.700	1.00 20.75	7
ATOM	1420	CA	VAL	460	14.082	20.862	69.026	1.00 22.58	6
ATOM	1421	CB	VAL	460	15.614	20.966	69.027	1.00 22.95	6
ATOM	1422	CG1	VAL	460	16.200	19.838	68.255	1.00 21.12	6
ATOM	1423	CG2	VAL	460	16.049	22.158	68.343	1.00 21.39	6
ATOM	1424	C	VAL	460	13.455	21.992	69.895	1.00 24.38	6
ATOM	1425	O	VAL	460	13.690	22.023	71.101	1.00 23.93	8
ATOM	1426	N	ASN	461	12.607	22.886	69.400	1.00 26.17	7
ATOM	1427	CA	ASN	461	12.179	23.921	70.338	1.00 30.11	6
ATOM	1428	CB	ASN	461	12.261	25.218	69.609	1.00 30.28	6
ATOM	1429	CG	ASN	461	13.524	25.827	69.822	1.00 32.22	6
ATOM	1430	OD1	ASN	461	13.852	26.115	70.970	1.00 36.22	8
ATOM	1431	ND2	ASN	461	14.323	25.957	68.790	1.00 31.57	7
ATOM	1432	C	ASN	461	10.807	23.602	70.759	1.00 32.15	6
ATOM	1433	O	ASN	461	10.001	24.451	71.252	1.00 32.31	8
ATOM	1434	N	ASP	462	10.332	22.748	70.981	1.00 34.41	7
ATOM	1435	CA	ASP	462	9.301	22.093	70.393	1.00 38.60	6
ATOM	1436	CB	ASP	462	9.831	20.690	70.133	1.00 43.46	6
ATOM	1437	CG	ASP	462	9.147	20.102	69.040	1.00 45.47	6
ATOM	1438	OD1	ASP	462	7.947	20.088	69.338	1.00 48.07	8
ATOM	1439	OD2	ASP	462	9.774	19.693	68.023	1.00 48.78	8
ATOM	1440	C	ASP	462	7.935	22.301	70.933	1.00 39.22	6
ATOM	1441	O	ASP	462	7.725	23.401	71.185	1.00 45.00	8
ATOM	1442	N	HIS	463	7.675	23.122	69.621	1.00 36.56	7
ATOM	1443	CA	HIS	463	6.541	23.070	68.712	1.00 33.62	6
ATOM	1444	CB	HIS	463	6.991	23.751	67.401	1.00 31.81	6
ATOM	1445	CG	HIS	463	7.354	25.182	67.597	1.00 31.93	6
ATOM	1446	CD2	HIS	463	6.554	26.267	67.716	1.00 28.93	6
ATOM	1447	ND1	HIS	463	8.640	25.610	67.888	1.00 31.28	7
ATOM	1448	CE1	HIS	463	8.600	26.901	68.194	1.00 30.44	6
ATOM	1449	NE2	HIS	463	7.347	27.314	68.100	1.00 32.05	7
ATOM	1450	C	HIS	463	5.867	21.710	68.406	1.00 31.10	6
ATOM	1451	O	HIS	463	6.502	20.681	68.088	1.00 30.85	8
ATOM	1452	N	LYS	464	4.556	21.802	68.345	1.00 30.56	7
ATOM	1453	CA	LYS	464	3.763	20.625	68.138	1.00 30.42	6
ATOM	1454	CB	LYS	464	2.625	20.762	69.095	1.00 34.48	6
ATOM	1455	CG	LYS	464	2.211	19.488	69.691	1.00 40.34	6
ATOM	1456	CD	LYS	464	1.104	19.723	70.752	1.00 45.18	6
ATOM	1457	CE	LYS	464	0.564	18.435	71.405	1.00 48.59	6
ATOM	1458	NZ	LYS	464	-0.666	18.796	72.297	1.00 50.10	7
ATOM	1459	C	LYS	464	3.270	20.485	66.705	1.00 26.40	6
ATOM	1460	O	LYS	464	2.397	21.272	66.251	1.00 26.68	8
ATOM	1461	N	PHE	465	3.799	19.499	66.018	1.00 23.27	7
ATOM	1462	CA	PHE	465	3.432	19.256	64.648	1.00 22.87	6
ATOM	1463	CB	PHE	465	4.560	18.496	63.972	1.00 19.62	6
ATOM	1464	CG	PHE	465	5.710	19.379	63.556	1.00 21.10	6
ATOM	1465	CD1	PHE	465	6.750	19.693	64.444	1.00 20.42	6
ATOM	1466	CD2	PHE	465	5.752	19.908	62.275	1.00 21.47	6
ATOM	1467	CE1	PHE	465	7.842	20.545	64.073	1.00 19.62	6

ATOM	1468	CE2	PHE	465	6.856	20.782	61.864	1.00 21.27	6
ATOM	1469	CZ	PHE	465	7.888	21.101	62.759	1.00 19.15	6
ATOM	1470	C	PHE	465	2.167	18.413	64.641	1.00 21.65	6
ATOM	1471	O	PHE	465	2.035	17.490	65.436	1.00 22.93	8
ATOM	1472	N	THR	466	1.242	18.736	63.760	1.00 21.55	7
ATOM	1473	CA	THR	466	0.009	18.002	63.671	1.00 21.21	6
ATOM	1474	CB	THR	466	-0.954	18.598	62.568	1.00 21.65	6
ATOM	1475	OG1	THR	466	-0.362	18.494	61.255	1.00 21.89	8
ATOM	1476	CG2	THR	466	-1.301	20.024	62.874	1.00 19.86	6
ATOM	1477	C	THR	466	0.308	16.553	63.278	1.00 21.47	6
ATOM	1478	O	THR	466	1.374	16.236	62.712	1.00 19.80	8
ATOM	1479	N	PRO	467	-0.660	15.661	63.538	1.00 22.08	7
ATOM	1480	CD	PRO	467	-1.768	15.767	64.521	1.00 24.47	6
ATOM	1481	CA	PRO	467	-0.390	14.268	63.156	1.00 21.12	6
ATOM	1482	CB	PRO	467	-1.624	13.475	63.644	1.00 20.85	6
ATOM	1483	CG	PRO	467	-2.536	14.481	64.343	1.00 24.34	6
ATOM	1484	C	PRO	467	-0.199	14.076	61.643	1.00 19.51	6
ATOM	1485	O	PRO	467	0.559	13.223	61.229	1.00 18.67	8
ATOM	1486	N	LEU	468	-0.885	14.876	60.826	1.00 19.19	7
ATOM	1487	CA	LEU	468	-0.676	14.754	59.387	1.00 18.12	6
ATOM	1488	CB	LEU	468	-1.684	15.618	58.619	1.00 21.41	6
ATOM	1489	CG	LEU	468	-1.440	15.809	57.120	1.00 22.59	6
ATOM	1490	CD1	LEU	468	-1.470	14.473	56.412	1.00 21.97	6
ATOM	1491	CD2	LEU	468	-2.617	16.705	56.545	1.00 24.15	6
ATOM	1492	C	LEU	468	0.781	15.179	59.027	1.00 17.01	6
ATOM	1493	O	LEU	468	1.440	14.484	58.250	1.00 15.29	8
ATOM	1494	N	LEU	469	1.292	16.274	59.602	1.00 14.97	7
ATOM	1495	CA	LEU	469	2.653	16.674	59.299	1.00 15.66	6
ATOM	1496	CB	LEU	469	2.934	18.106	59.744	1.00 15.55	6
ATOM	1497	CG	LEU	469	1.990	19.137	59.024	1.00 18.80	6
ATOM	1498	CD1	LEU	469	2.351	20.653	59.470	1.00 19.65	6
ATOM	1499	CD2	LEU	469	2.096	18.929	57.446	1.00 18.44	6
ATOM	1500	C	LEU	469	3.663	15.671	59.881	1.00 16.29	6
ATOM	1501	O	LEU	469	4.659	15.393	59.204	1.00 14.93	8
ATOM	1502	N	CYS	470	3.415	15.102	61.077	1.00 16.63	7
ATOM	1503	CA	CYS	470	4.372	14.101	61.630	1.00 17.51	6
ATOM	1504	CB	CYS	470	3.951	13.520	62.988	1.00 18.34	6
ATOM	1505	SG	CYS	470	4.008	14.791	64.298	1.00 25.58	16
ATOM	1506	C	CYS	470	4.515	12.931	60.667	1.00 20.22	6
ATOM	1507	O	CYS	470	5.623	12.422	60.466	1.00 18.40	8
ATOM	1508	N	GLU	471	3.428	12.571	59.892	1.00 19.96	7
ATOM	1509	CA	GLU	471	3.363	11.355	59.099	1.00 21.93	6
ATOM	1510	CB	GLU	471	1.911	11.018	58.720	1.00 24.55	6
ATOM	1511	CG	GLU	471	1.518	9.609	58.942	1.00 31.98	6
ATOM	1512	CD	GLU	471	2.618	8.598	58.646	1.00 30.87	6
ATOM	1513	OE1	GLU	471	2.695	8.036	57.520	1.00 32.35	8
ATOM	1514	OE2	GLU	471	3.396	8.354	59.578	1.00 34.47	8
ATOM	1515	C	GLU	471	4.137	11.489	57.763	1.00 20.36	6
ATOM	1516	O	GLU	471	4.884	10.588	57.364	1.00 20.19	8
ATOM	1517	N	ILE	472	3.733	12.796	57.307	1.00 19.78	7
ATOM	1518	CA	ILE	472	4.257	13.088	55.948	1.00 19.28	6
ATOM	1519	CB	ILE	472	3.380	14.106	55.185	1.00 21.54	6
ATOM	1520	CG2	ILE	472	4.025	14.453	53.749	1.00 20.47	6
ATOM	1521	CG1	ILE	472	2.062	13.436	54.771	1.00 25.47	6
ATOM	1522	CD1	ILE	472	1.330	12.803	55.835	1.00 31.00	6
ATOM	1523	C	ILE	472	5.683	13.534	55.929	1.00 18.52	6
ATOM	1524	O	ILE	472	6.438	13.142	55.016	1.00 17.85	8
ATOM	1525	N	TRP	473	6.065	14.282	56.951	1.00 17.41	7

ATOM	1526	CA	TRP	473	7.448	14.839	57.067	1.00	19.38	6
ATOM	1527	CB	TRP	473	7.380	16.275	57.566	1.00	19.90	6
ATOM	1528	CG	TRP	473	6.842	17.241	56.553	1.00	18.49	6
ATOM	1529	CD2	TRP	473	6.636	18.648	56.720	1.00	19.11	6
ATOM	1530	CE2	TRP	473	6.185	19.149	55.452	1.00	19.28	6
ATOM	1531	CE3	TRP	473	6.755	19.545	57.799	1.00	18.57	6
ATOM	1532	CD1	TRP	473	6.535	16.949	55.240	1.00	18.91	6
ATOM	1533	NE1	TRP	473	6.144	18.093	54.580	1.00	20.26	7
ATOM	1534	CZ2	TRP	473	5.911	20.506	55.243	1.00	18.78	6
ATOM	1535	CZ3	TRP	473	6.465	20.887	57.591	1.00	21.04	6
ATOM	1536	CH2	TRP	473	6.029	21.361	56.324	1.00	20.67	6
ATOM	1537	C	TRP	473	8.358	14.045	57.999	1.00	21.96	6
ATOM	1538	O	TRP	473	9.519	14.361	58.189	1.00	20.89	8
ATOM	1539	N	ASP	474	7.794	12.999	58.579	1.00	23.33	7
ATOM	1540	CA	ASP	474	8.488	12.138	59.483	1.00	26.65	6
ATOM	1541	CB	ASP	474	9.499	11.278	58.714	1.00	33.08	6
ATOM	1542	CG	ASP	474	8.865	9.992	58.227	1.00	37.35	6
ATOM	1543	OD1	ASP	474	9.302	8.900	58.653	1.00	44.86	8
ATOM	1544	OD2	ASP	474	7.877	10.049	57.468	1.00	42.64	8
ATOM	1545	C	ASP	474	9.107	12.853	60.659	1.00	26.85	6
ATOM	1546	O	ASP	474	10.290	12.712	60.916	1.00	26.66	8
ATOM	1547	N	VAL	475	8.285	13.622	61.373	1.00	26.36	7
ATOM	1548	CA	VAL	475	8.719	14.324	62.544	1.00	26.65	6
ATOM	1549	CB	VAL	475	8.665	15.867	62.355	1.00	27.22	6
ATOM	1550	CG1	VAL	475	9.530	16.315	61.145	1.00	26.80	6
ATOM	1551	CG2	VAL	475	7.193	16.320	62.177	1.00	24.70	6
ATOM	1552	C	VAL	475	7.710	13.915	63.642	1.00	29.66	6
ATOM	1553	O	VAL	475	6.773	13.094	63.410	1.00	27.46	8
ATOM	1554	OXT	VAL	475	7.809	14.473	64.750	1.00	33.53	8
ATOM	1	C1	FEX	1	6.578	24.730	58.626	1.00	22.38	6
ATOM	2	N1	FEX	1	6.458	24.174	60.065	1.00	20.26	7
ATOM	3	C2	FEX	1	5.227	23.546	60.618	1.00	20.19	6
ATOM	4	C3	FEX	1	7.894	24.485	60.743	1.00	20.55	6
ATOM	5	C4	FEX	1	7.783	25.403	57.967	1.00	24.19	6
ATOM	6	C5	FEX	1	7.734	25.896	56.610	1.00	22.43	6
ATOM	7	C6	FEX	1	6.502	25.781	55.813	1.00	24.06	6
ATOM	8	C7	FEX	1	5.306	25.108	56.466	1.00	23.96	6
ATOM	9	C8	FEX	1	5.354	24.611	57.822	1.00	22.08	6
ATOM	10	C9	FEX	1	6.522	26.238	54.715	1.00	25.61	6
ATOM	11	C10	FEX	1	5.223	26.851	54.327	1.00	26.67	6
ATOM	12	C11	FEX	1	5.011	27.479	53.086	1.00	27.33	6
ATOM	13	C12	FEX	1	6.093	27.546	52.148	1.00	27.57	6
ATOM	14	C13	FEX	1	7.326	26.980	52.489	1.00	28.27	6
ATOM	15	C14	FEX	1	7.553	26.343	53.721	1.00	26.97	6
ATOM	16	C15	FEX	1	5.993	28.218	50.808	1.00	29.22	6
ATOM	17	N2	FEX	1	5.061	29.111	50.445	1.00	30.16	7
ATOM	18	C16	FEX	1	3.889	28.787	49.996	1.00	33.64	6
ATOM	19	O1	FEX	1	3.450	27.529	49.815	1.00	33.87	8
ATOM	20	C17	FEX	1	5.733	30.473	50.853	1.00	28.79	6
ATOM	21	C18	FEX	1	6.736	31.223	50.098	1.00	26.38	6
ATOM	22	C19	FEX	1	7.260	32.491	50.540	1.00	25.49	6
ATOM	23	C20	FEX	1	6.796	33.078	51.764	1.00	26.55	6
ATOM	24	C21	FEX	1	5.822	32.406	52.583	1.00	27.70	6
ATOM	25	C22	FEX	1	5.295	31.098	52.109	1.00	27.63	6
ATOM	26	C23	FEX	1	5.226	32.596	53.733	1.00	29.18	6
ATOM	27	C24	FEX	1	4.905	32.093	54.942	1.00	30.89	6
ATOM	28	C25	FEX	1	5.121	32.873	56.142	1.00	30.54	6
ATOM	29	O2	FEX	1	4.366	32.387	57.318	1.00	29.43	8

```
ATOM     30  O3  FEX     1       5.940  34.001  56.319  1.00 31.02   8
ATOM     31  C26 FEX     1       4.574  33.117  58.506  1.00 30.57   6
ATOM     32  C27 FEX     1       3.118  29.861  49.757  1.00 34.18   6
ATOM     33  C28 FEX     1       1.681  29.914  50.605  1.00 36.36   6
ATOM     34  C29 FEX     1       0.795  31.179  50.327  1.00 36.77   6
ATOM     35  C30 FEX     1       0.325  31.610  48.701  1.00 36.95   6
ATOM     36  C31 FEX     1       1.715  31.463  47.837  1.00 35.29   6
ATOM     37  C32 FEX     1       2.796  30.288  48.187  1.00 36.97   6
END
```

APPENDIX 2

Up Regulated Genes with Treatment Fex:		
Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_004617	11.90	"HOMO SAPIENS TRANSMEMBRANE 4 SUPERFAMILY MEMBER 4 (TM4SF4), MRNA."
NM_003195	10.29	"HOMO SAPIENS TRANSCRIPTION ELONGATION FACTOR A (SII), 2 (TCEA2), MRNA."
NM_000893	9.17	"HOMO SAPIENS KININOGEN (KNG), MRNA."
NM_138961	6.12	"HOMO SAPIENS SIMILAR TO ENDOTHELIAL CELL-SELECTIVE ADHESION MOLECULE (ESAM), MRNA"
NM_139284	4.53	"HOMO SAPIENS LEUCINE-RICH REPEAT LGI FAMILY, MEMBER 4 (LGI4), MRNA"
AP000501	4.12	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 8P11.2, CLONE:91H23 TO 9-41"
NM_000394	3.96	"HOMO SAPIENS CRYSTALLIN, ALPHA A (CRYAA), MRNA."
BM701748	3.78	UI-E-CQ1-AEW-L-18-0-UI.R1 HOMO SAPIENS CDNA 5' END
NM_006209	3.64	"HOMO SAPIENS ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 2 (AUTOTAXIN) (ENPP2), MRNA."
NM_018602	3.39	"HOMO SAPIENS DNAJ (HSP40) HOMOLOG, SUBFAMILY A, MEMBER 4 (DNAJA4), MRNA"
AA442232	3.32	"ZV60H08.R1 SOARES_TESTIS_NHT HOMO SAPIENS CDNA CLONE IMAGE:758079 5', MRNA SEQUENCE"
NM_031916	3.28	"HOMO SAPIENS AKAP-ASSOCIATED SPERM PROTEIN (ASP), MRNA."
NM_022148	3.15	"HOMO SAPIENS CYTOKINE RECEPTOR-LIKE FACTOR 2 (CRLF2), MRNA"
NM_024935	3.14	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ13687 (FLJ13687), MRNA"
NM_032866	3.11	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ14957 (FLJ14957), MRNA."
NM_032471	3.02	"HOMO SAPIENS PROTEIN KINASE (CAMP-DEPENDENT, CATALYTIC) INHIBITOR BETA (PKIB), MRNA."
NM_013370	3.00	"HOMO SAPIENS PREGNANCY-INDUCED GROWTH INHIBITOR (OKL38), MRNA."
AL163259	2.99	NULL
NM_000151	2.83	"HOMO SAPIENS GLUCOSE-6-PHOSPHATASE, CATALYTIC (GLYCOGEN STORAGE DISEASE TYPE I, VON GIERKE DISEASE) (G6PC), MRNA."
NM_020689	2.78	"HOMO SAPIENS SODIUM CALCIUM EXCHANGER (NCKX3), MRNA."
NM_021098	2.71	"HOMO SAPIENS CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA 1H SUBUNIT (CACNA1H), MRNA"
NM_024984	2.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12193 (FLJ12193), MRNA"
NM_021778	2.65	"HOMO SAPIENS A DISINTEGRIN AND METALLOPROTEINASE DOMAIN 28 (ADAM28), TRANSCRIPT VARIANT 2, MRNA."
AF123462	2.59	"HOMO SAPIENS BAC526N18 NEUREXIN III GENE, PARTIAL CDS"
129456.1	2.59	NULL
AB020858	2.56	"HOMO SAPIENS GENOMIC DNA OF 8P21.3-P22 ANTI-ONCOGENE OF HEPATOCELLULAR COLORECTAL AND NON-SMALL CELL LUNG CANCER , SEGMENT 1/11"
NM_016445	2.56	"HOMO SAPIENS PLECKSTRIN 2 (MOUSE) HOMOLOG (PLEK2), MRNA."
NM_003614	2.53	"HOMO SAPIENS GALANIN RECEPTOR 3 (GALR3), MRNA."
NM_145047	2.49	"HOMO SAPIENS OXIDORED-NITRO DOMAIN-CONTAINING PROTEIN (NOR1), MRNA"
NM_001552	2.45	"HOMO SAPIENS INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 4 (IGFBP4), MRNA"
AB002366	2.42	"HUMAN MRNA FOR KIAA0368 GENE, PARTIAL CDS"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_031957	2.41	"HOMO SAPIENS KERATIN ASSOCIATED PROTEIN 1.5 (KRTAP1.5), MRNA"
NM_020659	2.38	"HOMO SAPIENS TWEETY HOMOLOG 1 (DROSOPHILA) (TTYH1), MRNA."
AB028998	2.37	"HOMO SAPIENS MRNA FOR KIAA1075 PROTEIN, PARTIAL CDS"
NM_001678	2.36	"HOMO SAPIENS ATPASE, NA+/K+ TRANSPORTING, BETA 2 POLYPEPTIDE (ATP1B2), MRNA."
NM_014375	2.35	"HOMO SAPIENS FETUIN B (FETUB), MRNA."
NM_000361	2.33	"HOMO SAPIENS THROMBOMODULIN (THBD), MRNA."
NM_004259	2.33	"HOMO SAPIENS RECQ PROTEIN-LIKE 5 (RECQL5), MRNA."
NM_000106	2.33	"HOMO SAPIENS CYTOCHROME P450, SUBFAMILY IID (DEBRISOQUINE, SPARTEINE, ETC., -METABOLIZING), POLYPEPTIDE 6 (CYP2D6), MRNA."
NM_003742	2.31	"HOMO SAPIENS ATP-BINDING CASSETTE, SUB-FAMILY B (MDR/TAP), MEMBER 11 (ABCB11), MRNA."
NM_003044	2.28	"HOMO SAPIENS SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, BETAINE/GABA), MEMBER 12 (SLC6A12), MRNA."
NM_001546	2.27	"HOMO SAPIENS INHIBITOR OF DNA BINDING 4, DOMINANT NEGATIVE HELIX-LOOP-HELIX PROTEIN (ID4), MRNA"
AF069061	2.25	"HOMO SAPIENS GLCNAC-1-P TRANSFERASE GENE, EXONS 1 THROUGH 4"
NM_012444	2.25	"HOMO SAPIENS SPO11 MEIOTIC PROTEIN COVALENTLY BOUND TO DSB-LIKE (S. CEREVISIAE) (SPO11), MRNA"
NM_000901	2.24	"HOMO SAPIENS NUCLEAR RECEPTOR SUBFAMILY 3, GROUP C, MEMBER 2 (NR3C2), MRNA."
AK027705	2.22	"HOMO SAPIENS CDNA FLJ14799 FIS, CLONE NT2RP4001351, WEAKLY SIMILAR TO HUMAN OVARIAN CANCER DOWNREGULATED MYOSIN HEAVY CHAIN HOMOLOG (DOC1) MRNA"
NM_052890	2.20	"HOMO SAPIENS PEPTIDOGLYCAN RECOGNITION PROTEIN L PRECURSOR (PGLYRP), MRNA"
NM_018379	2.19	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ11280 (FLJ11280), MRNA"
NM_005434	2.19	"HOMO SAPIENS BENE PROTEIN (BENE), MRNA"
NM_004183	2.18	"HOMO SAPIENS VITELLIFORM MACULAR DYSTROPHY (BEST DISEASE, BESTROPHIN) (VMD2), MRNA"
NM_005141	2.18	"HOMO SAPIENS FIBRINOGEN, B BETA POLYPEPTIDE (FGB), MRNA."
NM_001496	2.16	"HOMO SAPIENS GDNF FAMILY RECEPTOR ALPHA 3 (GFRA3), MRNA."
NM_003240	2.15	"HOMO SAPIENS ENDOMETRIAL BLEEDING ASSOCIATED FACTOR (LEFT-RIGHT DETERMINATION, FACTOR A; TRANSFORMING GROWTH FACTOR BETA SUPERFAMILY) (EBAF), MRNA."
NM_032413	2.14	"HOMO SAPIENS NORMAL MUCOSA OF ESOPHAGUS SPECIFIC 1 (NMES1), MRNA"
BC035779	2.14	"HOMO SAPIENS, SIMILAR TO SOLUTE CARRIER FAMILY 9 (SODIUM/HYDROGEN EXCHANGER), ISOFORM 7, CLONE MGC:46316 IMAGE:5590356, MRNA, COMPLETE CDS"
NM_021949	2.13	"HOMO SAPIENS ATPASE, CA++ TRANSPORTING, PLASMA MEMBRANE 3 (ATP2B3), MRNA."
BE348404	2.12	"HW17D06.X1 HOMO SAPIENS CDNA, 3' END"
NM_021233	2.12	"HOMO SAPIENS DNASE II-LIKE ACID DNASE (DLAD), TRANSCRIPT VARIANT 1, MRNA"
NM_004669	2.12	"HOMO SAPIENS CHLORIDE INTRACELLULAR CHANNEL 3 (CLIC3), MRNA."
NM_015685	2.12	"HOMO SAPIENS SYNDECAN BINDING PROTEIN (SYNTENIN) 2 (SDCBP2), MRNA."
NM_014945	2.11	"HOMO SAPIENS KIAA0843 PROTEIN (KIAA0843), MRNA."
X98507	2.11	H.SAPIENS MRNA FOR MYOSIN-I BETA
AK056268	2.11	"HOMO SAPIENS CDNA FLJ31706 FIS, CLONE NT2RI2006210, MODERATELY SIMILAR TO MUS MUSCULUS SHD MRNA"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AL137400	2.10	HOMO SAPIENS MRNA; CDNA DKFZP434L162 (FROM CLONE DKFZP434L162)
NM_000808	2.09	"HOMO SAPIENS GAMMA-AMINOBUTYRIC ACID (GABA) A RECEPTOR, ALPHA 3 (GABRA3), MRNA."
1387891.1	2.09	NULL
AF260225	2.08	"HOMO SAPIENS TESTIN 2 AND TESTIN 3 GENES, COMPLETE CDS, ALTERNATIVELY SPLICED"
NM_007163	2.08	"HOMO SAPIENS SOLUTE CARRIER FAMILY 14 (UREA TRANSPORTER), MEMBER 2 (SLC14A2), MRNA."
AB046859	2.08	"HOMO SAPIENS MRNA FOR KIAA1639 PROTEIN, PARTIAL CDS"
NM_002022	2.07	"HOMO SAPIENS FLAVIN CONTAINING MONOOXYGENASE 4 (FMO4), MRNA."
NM_000366	2.06	"HOMO SAPIENS TROPOMYOSIN 1 (ALPHA) (TPM1), MRNA"
NM_021146	2.06	"HOMO SAPIENS ANGIOPOIETIN-LIKE FACTOR (CTD6), MRNA."
NM_031961	2.06	"HOMO SAPIENS KERATIN ASSOCIATED PROTEIN 9.2 (KRTAP9.2), MRNA"
NM_005971	2.06	"HOMO SAPIENS FXYD DOMAIN-CONTAINING ION TRANSPORT REGULATOR 3 (FXYD3), TRANSCRIPT VARIANT 1, MRNA"
AK026600	2.05	"HOMO SAPIENS CDNA: FLJ22947 FIS, CLONE KAT09234"
NM_012277	2.05	"HOMO SAPIENS PANCREATIC BETA CELL GROWTH FACTOR (INGAP), MRNA."
S71547	2.04	"{ECCDNA 24, EXTRACHROMOSOMAL CIRCULAR DNA} [HUMAN, HELA S3 CELLS, GENOMIC, 806 NT]"
NM_002625	2.04	"HOMO SAPIENS 6-PHOSPHOFRUCTO-2-KINASE/FRUCTOSE-2,6-BIPHOSPHATASE 1 (PFKFB1), MRNA."
U71218	2.04	"HUMAN CLONE C74F4, 24KB PROXIMAL CMT1A-REP SEQUENCE"
AA427982	2.03	"HUMAN KRUPPEL RELATED ZINC FINGER PROTEIN (HTF10) MRNA, COMPLETE CDS."
NM_014242	2.02	"HOMO SAPIENS ZINC FINGER PROTEIN 237 (ZNF237), MRNA."
AF070586	2.02	HOMO SAPIENS CLONE 24528 MRNA SEQUENCE
NM_000482	2.01	"HOMO SAPIENS APOLIPOPROTEIN A-IV (APOA4), MRNA"
M30894	2.00	"GNL|UG|HS#S3370 HUMAN T-CELL RECEPTOR TI REARRANGED GAMMA CHAIN MRNA V-J-C REGION, COMPLETE CDS /CDS=(140,1156) /GB=M30894 /GI=339406 /UG=HS.112259 /LEN=1586"
BC016979	2.00	"HOMO SAPIENS, CLONE MGC:21802 IMAGE:4181575, MRNA, COMPLETE CDS"
NM_002666	1.99	"HOMO SAPIENS PERILIPIN (PLIN), MRNA."
NM_144659	1.98	"HOMO SAPIENS T-COMPLEX 10A-2 (LOC140290), MRNA"
NM_006160	1.97	"HOMO SAPIENS NEUROGENIC DIFFERENTIATION 2 (NEUROD2), MRNA."
AL137581	1.97	HOMO SAPIENS MRNA; CDNA DKFZP434B0610 (FROM CLONE DKFZP434B0610); PARTIAL CDS
BC024316	1.97	"HOMO SAPIENS, CLONE IMAGE:3912859, MRNA"
AL049328	1.97	HOMO SAPIENS MRNA; CDNA DKFZP564E026 (FROM CLONE DKFZP564E026)
NM_017734	1.96	"HOMO SAPIENS PALMDELPHIN (PALMD), MRNA."
AK022620	1.96	"HOMO SAPIENS CDNA FLJ12558 FIS, CLONE NT2RM4000787"
NM_000873	1.95	"HOMO SAPIENS INTERCELLULAR ADHESION MOLECULE 2 (ICAM2), MRNA"
U84003	1.95	"HOMO SAPIENS BRIDGING INTEGRATOR PROTEIN-1 (BIN1) GENE, EXONS 7-12"
NM_052962	1.95	"HOMO SAPIENS CLASS II CYTOKINE RECEPTOR (IL22RA2), MRNA"
NM_015577	1.95	"HOMO SAPIENS RETINOIC ACID INDUCED 14 (RAI14), MRNA."
NM_144626	1.93	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC17299 (MGC17299), MRNA"
AF217965	1.93	HOMO SAPIENS CLONE PP102 UNKNOWN MRNA
NM_002701	1.93	"HOMO SAPIENS POU DOMAIN, CLASS 5, TRANSCRIPTION FACTOR 1 (POU5F1), MRNA."
NM_031418	1.93	"HOMO SAPIENS CHROMOSOME 11 OPEN READING FRAME 25 (C11ORF25), MRNA."

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_013391	1.93	"HOMO SAPIENS DIMETHYLGLYCINE DEHYDROGENASE PRECURSOR (DMGDH), MRNA."
U82670	1.93	"HOMO SAPIENS XQ28 OF HIGH-MOBILITY GROUP PROTEIN 17 RETROPSEUDOGENE (PSHMG17), COMPLETE SEQUENCE; AND MELANOMA ANTIGEN FAMILY A1 (MAGEA1) AND ZINC FINGER PROTEIN 275 (ZNF275) GENES, COMPLETE CDS"
NM_000964	1.93	"HOMO SAPIENS RETINOIC ACID RECEPTOR, ALPHA (RARA), MRNA"
S70612	1.92	"GLYCINE TRANSPORTER TYPE 1C {ALTERNATIVELY SPLICED} [HUMAN, SUBSTANTIA NIGRA, MRNA, 2202 NT]"
AK021786	1.92	"HOMO SAPIENS CDNA FLJ11724 FIS, CLONE HEMBA1005331"
Y15067	1.91	HOMO SAPIENS MRNA FOR ZN-FINGER PROTEIN ZNF232
AL110262	1.91	HOMO SAPIENS MRNA; CDNA DKFZP586F0221 (FROM CLONE DKFZP586F0221)
Z64378	1.91	"H.SAPIENS CPG ISLAND DNA GENOMIC MSE1 FRAGMENT, CLONE 114F7, REVERSE READ CPG114F7.RT1A"
AW963947	1.91	EST376020 HOMO SAPIENS CDNA
NM_001767	1.91	"HOMO SAPIENS CD2 ANTIGEN (P50), SHEEP RED BLOOD CELL RECEPTOR (CD2), MRNA"
U41384	1.91	"HUMAN SMALL NUCLEAR RIBONUCLEAR PROTEIN ASSOCIATED POLYPEPTIDE N (SNRPN) GENE AND PRADER-WILLI SYNDROME GENE, COMPLETE SEQUENCE."
NM_012320	1.90	"HOMO SAPIENS LYSOPHOSPHOLIPASE 3 (LYSOSOMAL PHOSPHOLIPASE A2) (LYPLA3), MRNA"
AB011116	1.90	"HOMO SAPIENS MRNA FOR KIAA0544 PROTEIN, PARTIAL CDS"
NM_018915	1.89	"HOMO SAPIENS PROTOCADHERIN GAMMA SUBFAMILY A, 2 (PCDHGA2), TRANSCRIPT VARIANT 1, MRNA"
NM_003157	1.89	"HOMO SAPIENS SERINE/THREONINE KINASE 2 (STK2), MRNA."
NM_004072	1.89	"HOMO SAPIENS CHEMOKINE-LIKE RECEPTOR 1 (CMKLR1), MRNA."
AK001546	1.89	"HOMO SAPIENS CDNA FLJ10684 FIS, CLONE NT2RP3000220"
NM_014151	1.88	"HOMO SAPIENS HSPC053 PROTEIN (HSPC053), MRNA"
449023.1	1.88	NULL
NM_032259	1.88	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP434F054 (DKFZP434F054), MRNA"
NM_001169	1.88	"HOMO SAPIENS AQUAPORIN 8 (AQP8), MRNA."
X79535	1.88	"HUMAN MRNA FOR BETA TUBULIN, CLONE NUK_278."
U10689	1.87	"HUMAN MAGE-5A ANTIGEN (MAGE5A) GENE, COMPLETE CDS"
AF324499	1.87	"HOMO SAPIENS OLFACTORY-LIKE RECEPTOR MRNA, COMPLETE CDS"
AL133659	1.87	HOMO SAPIENS MRNA; CDNA DKFZP434K0227 (FROM CLONE DKFZP434K0227); PARTIAL CDS
NM_032962	1.86	"HOMO SAPIENS SMALL INDUCIBLE CYTOKINE SUBFAMILY A (CYS-CYS), MEMBER 14 (SCYA14), TRANSCRIPT VARIANT 2, MRNA."
BC013181	1.86	"HOMO SAPIENS, CLONE MGC:21682 IMAGE:4385873, MRNA, COMPLETE CDS"
NM_019038	1.86	"HOMO SAPIENS HYPOTHETICAL PROTEIN (FLJ11045), MRNA."
W89128	1.86	"ZH69C04.S1 HOMO SAPIENS CDNA, 3' END"
1327919.2	1.85	NULL
NM_005165	1.85	"HOMO SAPIENS ALDOLASE C, FRUCTOSE-BISPHOSPHATE (ALDOC), MRNA."
NM_014037	1.85	"HOMO SAPIENS NTT5 PROTEIN (NTT5), MRNA."
H10529	1.85	"YM04A08.R1 HOMO SAPIENS CDNA, 5' END"
NM_032687	1.85	PROTEIN OF UNKNOWN FUNCTION
AJ292466	1.84	"HOMO SAPIENS MRNA FOR WDR9 PROTEIN (WDR9 GENE), FORM B"
NM_002190	1.84	"HOMO SAPIENS INTERLEUKIN 17 (CYTOTOXIC T-LYMPHOCYTE-ASSOCIATED SERINE ESTERASE 8) (IL17), MRNA."
AF191622	1.84	"HOMO SAPIENS FILAMIN (FLNB) GENE, EXON 35"
NM_052863	1.84	"HOMO SAPIENS SECRETOGLOBIN, FAMILY 3A, MEMBER 1 (SCGB3A1), MRNA"
201531.1	1.84	NULL

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_001727	1.83	"HOMO SAPIENS BOMBESIN-LIKE RECEPTOR 3 (BRS3), MRNA"
X63578	1.83	H.SAPIENS GENE FOR PARVALBUMIN
NM_014897	1.83	"HOMO SAPIENS KIAA0924 PROTEIN (KIAA0924), MRNA."
NM_031200	1.83	"HOMO SAPIENS CHEMOKINE (C-C MOTIF) RECEPTOR 9 (CCR9), TRANSCRIPT VARIANT A, MRNA."
AL157504	1.83	HOMO SAPIENS MRNA; CDNA DKFZP586O0724 (FROM CLONE DKFZP586O0724)
BC031087	1.83	"HOMO SAPIENS, SIMILAR TO GAMMA-AMINOBUTYRIC-ACID RECEPTOR GAMMA-1 SUBUNIT PRECURSOR (GABA(A) RECEPTOR), CLONE MGC:33838 IMAGE:5289008, MRNA, COMPLETE CDS"
NM_014461	1.81	"HOMO SAPIENS CONTACTIN 6 (CNTN6), MRNA."
AB047819	1.81	"HOMO SAPIENS GCMA/GCM1 GENE FOR CHORION-SPECIFIC TRANSCRIPTION FACTOR GCMA, COMPLETE CDS"
NM_003264	1.81	"HOMO SAPIENS TOLL-LIKE RECEPTOR 2 (TLR2), MRNA."
NM_000508	1.81	"HOMO SAPIENS FIBRINOGEN, A ALPHA POLYPEPTIDE (FGA), TRANSCRIPT VARIANT ALPHA-E, MRNA."
AK021635	1.81	"HOMO SAPIENS CDNA FLJ11573 FIS, CLONE HEMBA1003376"
NM_032211	1.80	"HOMO SAPIENS LYSYL OXIDASE-LIKE 4 (LOXL4), MRNA"
NM_033014	1.80	"HOMO SAPIENS OSTEOGLYCIN (OSTEOINDUCTIVE FACTOR, MIMECAN) (OGN), TRANSCRIPT VARIANT 1, MRNA."
AB020636	1.80	"HOMO SAPIENS MRNA FOR KIAA0829 PROTEIN, PARTIAL CDS"
AJ242910	1.80	HOMO SAPIENS MRNA FOR N-ACETYLGLUCOSAMINE KINASE
X52852	1.80	HUMAN CYCLOPHILIN-RELATED PROCESSED PSEUDOGENE
NM_014069	1.80	"HOMO SAPIENS SPR1 PROTEIN (SPR1), MRNA."
NM_032607	1.80	"HOMO SAPIENS CREB/ATF FAMILY TRANSCRIPTION FACTOR (CREB-H), MRNA"
1462881.1	1.79	"MEMBER OF THE RHODOPSIN FAMILY OF G PROTEIN-COUPLED RECEPTORS (GPCR), HAS MODERATE SIMILARITY TO OLFACTORY RECEPTOR 41 (MOUSE OLFR41), WHICH MAY HAVE A ROLE IN OLFACTORY RESPONSE AND INTERACTS PREFERENTIALLY WITH HEPTANAL"
AF300796	1.79	"HOMO SAPIENS SIALIC ACID-SPECIFIC 9-O-ACETYLESTERASE I MRNA, COMPLETE CDS"
NM_006204	1.79	"HOMO SAPIENS PHOSPHODIESTERASE 6C, CGMP-SPECIFIC, CONE, ALPHA PRIME (PDE6C), MRNA."
NM_033066	1.79	"HOMO SAPIENS MEMBRANE PROTEIN, PALMITOYLATED 4 (MAGUK P55 SUBFAMILY MEMBER 4) (MPP4), MRNA"
NM_000341	1.79	"HOMO SAPIENS SOLUTE CARRIER FAMILY 3 (CYSTINE, DIBASIC AND NEUTRAL AMINO ACID TRANSPORTERS, ACTIVATOR OF CYSTINE, DIBASIC AND NEUTRAL AMINO ACID TRANSPORT), MEMBER 1 (SLC3A1), MRNA."
1452359.3	1.78	NULL
AL080103	1.78	HOMO SAPIENS MRNA; CDNA DKFZP564N2216 (FROM CLONE DKFZP564N2216)
D86992	1.78	"HOMO SAPIENS IMMUNOGLOBULIN LAMBDA GENE LOCUS DNA, CLONE:123E1 UPSTREAM CONTIG"
NM_021038	1.78	"HOMO SAPIENS MUSCLEBLIND-LIKE (DROSOPHILA) (MBNL), MRNA."
958731.1	1.78	"MEMBER OF THE SHORT-CHAIN DEHYDROGENASE-REDUCTASE FAMILY, HAS A REGION OF LOW SIMILARITY TO 11 BETA-HYDROXYSTEROID DEHYDROGENASE (MOUSE HSD11B1), WHICH IS A MICROSOMAL CARBONYL REDUCTASE THAT HAS 11 BETA-DEHYDROGENASE AND 11-OXO REDUCTASE ACTIVITY"
NM_021135	1.77	"HOMO SAPIENS RIBOSOMAL PROTEIN S6 KINASE, 90KD, POLYPEPTIDE 2 (RPS6KA2), MRNA"
NM_000773	1.77	"HOMO SAPIENS CYTOCHROME P450, SUBFAMILY IIE (ETHANOL-INDUCIBLE) (CYP2E), MRNA."
NM_000487	1.77	"HOMO SAPIENS ARYLSULFATASE A (ARSA), MRNA."
AL049431	1.77	HOMO SAPIENS MRNA; CDNA DKFZP586J211 (FROM CLONE DKFZP586J211)

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AW406117	1.76	"HUMAN LAMBDA CLONE 247 FRA3B REGION DNA, CYCLOPHILIN PSEUDOGENE, PARTIAL SEQUENCE, AND HPV16 VIRAL INTEGRATION SITE."
NM_002934	1.76	"HOMO SAPIENS RIBONUCLEASE, RNASE A FAMILY, 2 (LIVER, EOSINOPHIL-DERIVED NEUROTOXIN) (RNASE2), MRNA"
NM_001347	1.76	"HOMO SAPIENS DIACYLGLYCEROL KINASE, THETA (110KD) (DGKQ), MRNA"
AB023173	1.76	"HOMO SAPIENS MRNA FOR KIAA0956 PROTEIN, PARTIAL CDS"
BC025726	1.76	"HOMO SAPIENS, POTASSIUM CHANNEL, SUBFAMILY K, MEMBER 17 (TASK-4), CLONE MGC:34117 IMAGE:5201326, MRNA, COMPLETE CDS"
AB001517	1.76	"HOMO SAPIENS DNA FOR TMEM1 PROTEIN, PWP2 PROTEIN, KNP-I ALPHA PROTEIN AND KNP-I BETA PROTEIN, PARTIAL AND COMPLETE CDS"
U28480	1.76	"HUMAN UNCOUPLING PROTEIN (UCP) MRNA, COMPLETE CDS"
NM_002881	1.75	"HOMO SAPIENS V-RAL SIMIAN LEUKEMIA VIRAL ONCOGENE HOMOLOG B (RAS RELATED; GTP BINDING PROTEIN) (RALB), MRNA."
NM_021871	1.75	"HOMO SAPIENS FIBRINOGEN, A ALPHA POLYPEPTIDE (FGA), TRANSCRIPT VARIANT ALPHA, MRNA"
NM_032989	1.75	"HOMO SAPIENS BCL2-ANTAGONIST OF CELL DEATH (BAD), TRANSCRIPT VARIANT 2, MRNA."
NM_003960	1.75	"HOMO SAPIENS KIDNEY- AND LIVER-SPECIFIC GENE (CML1), MRNA."
NM_014693	1.75	"HOMO SAPIENS ENDOTHELIN CONVERTING ENZYME 2 (ECE2), MRNA."
NM_001323	1.74	"HOMO SAPIENS CYSTATIN E/M (CST6), MRNA."
AL832363	1.74	HOMO SAPIENS MRNA; CDNA DKFZP451N156 (FROM CLONE DKFZP451N156)
NM_003272	1.74	"HOMO SAPIENS TRANSMEMBRANE 7 SUPERFAMILY MEMBER 1 (UPREGULATED IN KIDNEY) (TM7SF1), MRNA."
NM_005018	1.74	"HOMO SAPIENS PROGRAMMED CELL DEATH 1 (PDCD1), MRNA."
AK057674	1.74	"HOMO SAPIENS CDNA FLJ33112 FIS, CLONE TRACH2001109"
AI797481	1.74	WE88E01.X1 HOMO SAPIENS CDNA 3' END
NM_014965	1.74	"HOMO SAPIENS KIAA1042 PROTEIN (KIAA1042), MRNA."
NM_004570	1.73	"HOMO SAPIENS PHOSPHOINOSITIDE-3-KINASE, CLASS 2, GAMMA POLYPEPTIDE (PIK3C2G), MRNA."
AK025583	1.73	"HOMO SAPIENS CDNA: FLJ21930 FIS, CLONE HEP04301, HIGHLY SIMILAR TO HSU90916 HUMAN CLONE 23815 MRNA SEQUENCE"
1397221.43	1.73	NULL
AF345906	1.73	"HOMO SAPIENS LIM MINERALIZATION PROTEIN 3 MRNA, COMPLETE CDS"
NM_032642	1.73	"HOMO SAPIENS WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 5B (WNT5B), TRANSCRIPT VARIANT 1, MRNA."
1329470.331	1.73	NULL
M61170	1.73	"HUMAN POLYMORPHIC EPITHELIAL MUCIN (PEM) GENE, COMPLETE CDS"
NM_000627	1.73	"HOMO SAPIENS LATENT TRANSFORMING GROWTH FACTOR BETA BINDING PROTEIN 1 (LTBP1), MRNA."
NM_145276	1.72	"HOMO SAPIENS SIMILAR TO KRUPPEL-TYPE ZINC FINGER (C2H2) (LOC147837), MRNA"
1353408.4	1.72	NULL
AF052160	1.72	HOMO SAPIENS CLONE 24629 MRNA SEQUENCE
NM_002600	1.72	"HOMO SAPIENS PHOSPHODIESTERASE 4B, CAMP-SPECIFIC (PHOSPHODIESTERASE E4 DUNCE HOMOLOG, DROSOPHILA) (PDE4B), MRNA."
D28877	1.72	"HOMO SAPIENS HNRPA2B1 GENE FOR HNRNP PROTEIN A2 AND B1, COMPLETE CDS"
AK022354	1.71	"HOMO SAPIENS CDNA FLJ12292 FIS, CLONE MAMMA1001812"
NM_003734	1.71	"HOMO SAPIENS AMINE OXIDASE, COPPER CONTAINING 3 (VASCULAR ADHESION PROTEIN 1) (AOC3), MRNA."

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_004921	1.71	"HOMO SAPIENS CHLORIDE CHANNEL, CALCIUM ACTIVATED, FAMILY MEMBER 3 (CLCA3), MRNA"
BC034709	1.71	"HOMO SAPIENS, SIMILAR TO GAP JUNCTION BETA-4 PROTEIN (CONNEXIN 30.3) (CX30.3), CLONE MGC:21116 IMAGE:4755173, MRNA, COMPLETE CDS"
NM_014912	1.71	"HOMO SAPIENS KIAA0940 PROTEIN (KIAA0940), MRNA."
NM_018639	1.70	"HOMO SAPIENS CS BOX-CONTAINING WD PROTEIN (LOC55884), MRNA."
979318.3	1.70	"PROTEIN CONTAINING 11 LEUCINE RICH REPEATS, WHICH MEDIATE PROTEIN-PROTEIN INTERACTIONS, HAS A REGION OF LOW SIMILARITY TO HUMAN IGFALS, WHICH IS ACID-LABILE SUBUNIT OF THE INSULIN-LIKE GROWTH FACTOR (IGF) BINDING PROTEIN THAT MAY MODULATE IGF ACTIVITY"
AK024603	1.70	"HOMO SAPIENS CDNA: FLJ20950 FIS, CLONE ADSE01927"
NM_022370	1.70	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ21044 SIMILAR TO RBIG1 (FLJ21044), MRNA"
NM_014954	1.70	"HOMO SAPIENS KIAA0985 PROTEIN (KIAA0985), MRNA."
M64497	1.70	"HUMAN APOLIPOPROTEIN AI REGULATORY PROTEIN (ARP-1) MRNA, COMPLETE CDS"
AB032986	1.70	"HOMO SAPIENS MRNA FOR KIAA1160 PROTEIN, PARTIAL CDS"
AK094585	1.70	"HOMO SAPIENS CDNA FLJ37266 FIS, CLONE BRAMY2011280"
NM_018592	1.69	"HOMO SAPIENS HYPOTHETICAL PROTEIN PRO0800 (PRO0800), MRNA"
AF222345	1.69	"HOMO SAPIENS SUPPRESSOR OF FUSED VARIANT 3 MRNA, ALTERNATIVELY SPLICED, COMPLETE CDS"
AJ420504	1.69	HOMO SAPIENS MRNA FULL LENGTH INSERT CDNA CLONE EUROIMAGE 2069692
NM_001656	1.69	"HOMO SAPIENS ADP-RIBOSYLATION FACTOR DOMAIN PROTEIN 1, 64KD (ARFD1), TRANSCRIPT VARIANT ALPHA, MRNA."
AA868513	1.69	"AK43C02.S1 HOMO SAPIENS CDNA, 3' END"
NM_012400	1.69	"HOMO SAPIENS PHOSPHOLIPASE A2, GROUP IID (PLA2G2D), MRNA."
NM_003662	1.69	"HOMO SAPIENS PIRIN (PIR), MRNA."
U41302	1.69	"HUMAN CHROMOSOME 16 CREATINE TRANSPORTER (SLC6A8) AND (CDM) PARALOGOUS GENES, COMPLETE CDS"
AU133056	1.69	"AU133056 HOMO SAPIENS CDNA, 5' END"
AB040903	1.69	"HOMO SAPIENS MRNA FOR KIAA1470 PROTEIN, PARTIAL CDS"
U17081	1.69	"HUMAN FATTY ACID BINDING PROTEIN (FABP3) GENE, COMPLETE CDS."
AB029001	1.68	"HOMO SAPIENS MRNA FOR KIAA1078 PROTEIN, PARTIAL CDS"
J03040	1.68	"HUMAN SPARC/OSTEONECTIN MRNA, COMPLETE CDS"
AK024251	1.68	"HOMO SAPIENS CDNA FLJ14189 FIS, CLONE NT2RP2006184, HIGHLY SIMILAR TO HOMO SAPIENS MRNA FOR KIAA0918 PROTEIN"
NM_004286	1.68	"HOMO SAPIENS GTP BINDING PROTEIN 1 (GTPBP1), MRNA"
NM_005980	1.68	"HOMO SAPIENS S100 CALCIUM BINDING PROTEIN P (S100P), MRNA."
NM_005953	1.68	"METALLOTHIONEIN 2A, FUNCTIONS IN METAL HOMEOSTASIS AND PROTECTS AGAINST HEAVY-METAL TOXICITY, MAY HAVE ROLES IN THE REGULATION OF CELLULAR PROLIFERATION, APOPTOSIS, AND MALIGNANT PROGRESSION"
AF195513	1.68	"HOMO SAPIENS PUR-GAMMA A-FORM (PURG) MRNA, COMPLETE CDS"
NM_003546	1.68	"HOMO SAPIENS H4 HISTONE FAMILY, MEMBER K (H4FK), MRNA"
NM_000869	1.67	"HOMO SAPIENS 5-HYDROXYTRYPTAMINE (SEROTONIN) RECEPTOR 3A (HTR3A), MRNA."
218630.6	1.67	PROTEIN OF UNKNOWN FUNCTION
NM_000217	1.67	"HOMO SAPIENS POTASSIUM VOLTAGE-GATED CHANNEL, SHAKER-RELATED SUBFAMILY, MEMBER 1 (EPISODIC ATAXIA WITH MYOKYMIA) (KCNA1), MRNA."
AB033030	1.67	"HOMO SAPIENS MRNA FOR KIAA1204 PROTEIN, PARTIAL CDS"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
BC012362	1.67	"HOMO SAPIENS, CLONE MGC:20484 IMAGE:4650072, MRNA, COMPLETE CDS"
AA001334	1.67	"ZH83C02.R1 HOMO SAPIENS CDNA, 5' END"
NM_001114	1.67	"HOMO SAPIENS ADENYLATE CYCLASE 7 (ADCY7), MRNA."
NM_006759	1.67	"HOMO SAPIENS UDP-GLUCOSE PYROPHOSPHORYLASE 2 (UGP2), MRNA."
NM_152270	1.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ34922 (FLJ34922), MRNA"
NM_025206	1.67	"HOMO SAPIENS FER-1-LIKE 4 (C. ELEGANS) (FER1L4), MRNA"
NM_031305	1.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP564B1162 (DKFZP564B1162), MRNA"
H09245	1.66	"YL98A12.S1 HOMO SAPIENS CDNA, 3' END"
1042260.1	1.66	NULL
NM_004950	1.66	"HOMO SAPIENS DERMATAN SULFATE PROTEOGLYCAN 3 (DSPG3), MRNA."
AB007969	1.66	"HOMO SAPIENS MRNA, CHROMOSOME 1 SPECIFIC TRANSCRIPT KIAA0500"
NM_000705	1.66	"HOMO SAPIENS ATPASE, H+/K+ EXCHANGING, BETA POLYPEPTIDE (ATP4B), MRNA."
NM_002965	1.66	"HOMO SAPIENS S100 CALCIUM BINDING PROTEIN A9 (CALGRANULIN B) (S100A9), MRNA"
NM_006149	1.66	"HOMO SAPIENS LECTIN, GALACTOSIDE-BINDING, SOLUBLE, 4 (GALECTIN 4) (LGALS4), MRNA"
AL163248	1.66	HOMO SAPIENS CHROMOSOME 21 SEGMENT HS21C048
AF009640	1.66	"HOMO SAPIENS CLONE 33 IMMUNOGLOBULIN-LIKE TRANSCRIPT 5 PROTEIN MRNA, COMPLETE CDS"
NM_017786	1.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20366 (FLJ20366), MRNA."
AF217796	1.66	"HOMO SAPIENS SCG10 LIKE-PROTEIN, HELICASE-LIKE PROTEIN NHL, M68, AND ADP-RIBOSYLATION FACTOR RELATED PROTEIN 1 (ARFRP1) GENES, COMPLETE CDS"
NM_015230	1.66	"HOMO SAPIENS CENTAURIN, DELTA 1 (CENTD1), MRNA."
NM_000802	1.66	"HOMO SAPIENS FOLATE RECEPTOR 1 (ADULT) (FOLR1), TRANSCRIPT VARIANT 1, MRNA"
BC014851	1.66	"HOMO SAPIENS, SIMILAR TO LUNATIC FRINGE GENE HOMOLOG (DROSOPHILA), CLONE MGC:22145 IMAGE:4453156, MRNA, COMPLETE CDS"
AK000789	1.66	"HOMO SAPIENS CDNA FLJ20782 FIS, CLONE COL03841"
NM_006810	1.66	"HOMO SAPIENS FOR PROTEIN DISULFIDE ISOMERASE-RELATED (PDIR), MRNA."
NM_030984	1.65	"HOMO SAPIENS THROMBOXANE A SYNTHASE 1 (PLATELET, CYTOCHROME P450, SUBFAMILY V) (TBXAS1), TRANSCRIPT VARIANT TXS-II, MRNA."
NM_145016	1.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC24009 (MGC24009), MRNA"
AK002122	1.65	"HOMO SAPIENS CDNA FLJ11260 FIS, CLONE PLACE1009060, WEAKLY SIMILAR TO BRO1 PROTEIN"
AB006627	1.65	"HOMO SAPIENS MRNA FOR KIAA0289 GENE, PARTIAL CDS"
AK022892	1.65	"HOMO SAPIENS CDNA FLJ12830 FIS, CLONE NT2RP2003073"
AF088219	1.65	"HUMAN CC CHEMOKINE GENE CLUSTER, COMPLETE SEQUENCE."
BC035035	1.65	"HOMO SAPIENS, SIMILAR TO ECTONUCLEOTIDE PYROPHOSPHATASE/PHOSPHODIESTERASE 5, CLONE MGC:33971 IMAGE:5259487, MRNA, COMPLETE CDS"
AF147791	1.65	"HOMO SAPIENS MUCIN 11 (MUC11) MRNA, PARTIAL CDS"
AU127911	1.65	AU127911 HOMO SAPIENS CDNA 5' END
L13738	1.65	"HOMO SAPIENS ACTIVATED P21CDC42HS KINASE (ACK1) MRNA, COMPLETE CDS"
U78027	1.65	"HOMO SAPIENS BRUTON'S TYROSINE KINASE (BTK), ALPHA-D-GALACTOSIDASE A (GLA), L44-LIKE RIBOSOMAL PROTEIN (L44L) AND FTP3 (FTP3) GENES, COMPLETE CDS"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AB037770	1.65	"HOMO SAPIENS MRNA FOR KIAA1349 PROTEIN, PARTIAL CDS"
AK025586	1.65	"HOMO SAPIENS CDNA: FLJ21933 FIS, CLONE HEP04337"
NM_138569	1.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC18257 (MGC18257), MRNA"
AB011542	1.65	"HOMO SAPIENS MRNA FOR MEGF9, PARTIAL CDS"
NM_015644	1.64	"HOMO SAPIENS DKFZP434B103 PROTEIN (DKFZP434B103), MRNA."
NM_012472	1.64	"HOMO SAPIENS TESTIS SPECIFIC LEUCINE RICH REPEAT PROTEIN (TSLRP), MRNA."
NM_031371	1.64	"HOMO SAPIENS RBP1-LIKE PROTEIN (BCAA), TRANSCRIPT VARIANT 2, MRNA."
AI766221	1.64	"WH68B09.X1 HOMO SAPIENS CDNA, 3' END"
NM_003878	1.64	"HOMO SAPIENS GAMMA-GLUTAMYL HYDROLASE (CONJUGASE, FOLYLPOLYGAMMAGLUTAMYL HYDROLASE) (GGH), MRNA."
NM_000761	1.64	"HOMO SAPIENS CYTOCHROME P450, SUBFAMILY I (AROMATIC COMPOUND-INDUCIBLE), POLYPEPTIDE 2 (CYP1A2), MRNA."
AL137595	1.64	HOMO SAPIENS MRNA; CDNA DKFZP434P0810 (FROM CLONE DKFZP434P0810)
AL543586	1.64	AL543586 HOMO SAPIENS CDNA
AW276618	1.64	"XR17C08.X1 HOMO SAPIENS CDNA, 3' END"
AK023156	1.64	"HOMO SAPIENS CDNA FLJ13094 FIS, CLONE NT2RP3002163"
NM_022768	1.64	"HOMO SAPIENS RNA BINDING MOTIF PROTEIN 15 (RBM15), MRNA"
NM_007150	1.64	"HOMO SAPIENS ZINC FINGER PROTEIN 185 (LIM DOMAIN) (ZNF185), MRNA."
AK024371	1.64	"HOMO SAPIENS CDNA FLJ14309 FIS, CLONE PLACE3000221"
AP003115	1.63	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 8Q23, CLONE: KB1000E4"
1401244.3	1.63	NULL
NM_000033	1.63	"HOMO SAPIENS ATP-BINDING CASSETTE, SUB-FAMILY D (ALD), MEMBER 1 (ABCD1), MRNA."
NM_005542	1.63	"HOMO SAPIENS INSULIN INDUCED GENE 1 (INSIG1), MRNA."
NM_004374	1.63	"HOMO SAPIENS CYTOCHROME C OXIDASE SUBUNIT VIC (COX6C), NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA"
NM_017878	1.63	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20556 (FLJ20556), MRNA."
NM_006214	1.63	"HOMO SAPIENS PHYTANOYL-COA HYDROXYLASE (REFSUM DISEASE) (PHYH), MRNA."
NM_006918	1.63	"HOMO SAPIENS STEROL-C5-DESATURASE (ERG3 DELTA-5-DESATURASE HOMOLOG, FUNGAL)-LIKE (SC5DL), MRNA"
NM_014629	1.63	"HOMO SAPIENS RHO GUANINE NUCLEOTIDE EXCHANGE FACTOR (GEF) 10 (ARHGEF10), MRNA."
U63721	1.63	"HUMAN ELASTIN (ELN) GENE, PARTIAL CDS, AND LIM-KINASE (LIMK1) GENE, COMPLETE CDS."
AU129688	1.63	AU129688 HOMO SAPIENS CDNA 5' END
AL122040	1.63	HOMO SAPIENS MRNA; CDNA DKFZP434G1972 (FROM CLONE DKFZP434G1972)
AL163263	1.63	NULL
NM_014029	1.63	"HOMO SAPIENS HSPC022 PROTEIN (HSPC022), MRNA"
NM_003554	1.62	"HOMO SAPIENS OLFACTORY RECEPTOR, FAMILY 1, SUBFAMILY E, MEMBER 2 (OR1E2), MRNA"
NM_015074	1.62	"HOMO SAPIENS KINESIN FAMILY MEMBER 1B (KIF1B), MRNA."
BC002575	1.62	"HOMO SAPIENS, CLONE IMAGE:3161568, MRNA, PARTIAL CDS"
NM_014131	1.62	"HOMO SAPIENS PRO0514 PROTEIN (PRO0514), MRNA"
AL163277	1.62	NULL
1455058.1	1.62	NULL
NM_022792	1.62	"HOMO SAPIENS MATRIX METALLOPROTEINASE 19 (MMP19), TRANSCRIPT VARIANT RASI-9, MRNA."
NM_020344	1.62	"HOMO SAPIENS SOLUTE CARRIER FAMILY 24 (SODIUM/POTASSIUM/CALCIUM EXCHANGER), MEMBER 2 (SLC24A2), MRNA"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_003980	1.62	"HOMO SAPIENS MICROTUBULE-ASSOCIATED PROTEIN 7 (MAP7), MRNA."
S57283	1.62	"HOMO SAPIENS ENDOTHELIN ET-B RECEPTOR MRNA, COMPLETE CDS"
NM_006564	1.62	"HOMO SAPIENS G PROTEIN-COUPLED RECEPTOR (TYMSTR), MRNA."
BC011693	1.62	"HOMO SAPIENS, CLONE IMAGE:3140802, MRNA"
AF117615	1.62	"HOMO SAPIENS HEME-BINDING PROTEIN (HBP) MRNA, COMPLETE CDS"
NM_002196	1.62	"HOMO SAPIENS INSULINOMA-ASSOCIATED 1 (INSM1), MRNA."
1044035.1	1.61	NULL
NM_000438	1.61	"HOMO SAPIENS PAIRED BOX GENE 3 (WAARDENBURG SYNDROME 1) (PAX3), TRANSCRIPT VARIANT PAX3A, MRNA"
NM_002405	1.61	"HOMO SAPIENS MANIC FRINGE HOMOLOG (DROSOPHILA) (MFNG), MRNA."
NM_006113	1.61	"HOMO SAPIENS VAV 3 ONCOGENE (VAV3), MRNA."
AL080148	1.61	HOMO SAPIENS MRNA; CDNA DKFZP434B204 (FROM CLONE DKFZP434B204); PARTIAL CDS
AK056569	1.61	"HOMO SAPIENS CDNA FLJ32007 FIS, CLONE NT2RP7009481, WEAKLY SIMILAR TO DROSOPHILA MELANOGASTER DISPATCHED MRNA"
NM_018104	1.61	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10474 (FLJ10474), MRNA."
NM_012339	1.61	"HOMO SAPIENS TRANSMEMBRANE 4 SUPERFAMILY MEMBER (TETRASPAN NET-7) (NET-7), MRNA."
NM_001684	1.61	"HOMO SAPIENS ATPASE, CA++ TRANSPORTING, PLASMA MEMBRANE 4 (ATP2B4), MRNA"
NM_016098	1.61	"HOMO SAPIENS HSPC040 PROTEIN (LOC51660), MRNA."
NM_002997	1.61	"HOMO SAPIENS SYNDECAN 1 (SDC1), MRNA."
AF098485	1.61	"HOMO SAPIENS NAPSIN 2 PRECURSOR, MRNA, PARTIAL SEQUENCE"
NM_006672	1.61	"HOMO SAPIENS SOLUTE CARRIER FAMILY 22 (ORGANIC ANION TRANSPORTER), MEMBER 7 (SLC22A7), MRNA."
BG476978	1.61	"HUMAN GENE FOR RYUDOCAN CORE PROTEIN, EXON1-5, COMPLETE CDS."
AL133568	1.61	HOMO SAPIENS MRNA; CDNA DKFZP434N197 (FROM CLONE DKFZP434N197)
NM_005588	1.60	"HOMO SAPIENS MEPRIN A, ALPHA (PABA PEPTIDE HYDROLASE) (MEP1A), MRNA."
NM_003943	1.60	"HOMO SAPIENS GENETHONIN 1 (GENX-3414), MRNA."
AC006017	1.60	"HUMAN ALR-LIKE PROTEIN MRNA, COMPLETE CDS."
AL080186	1.60	HOMO SAPIENS MRNA; CDNA DKFZP564B0769 (FROM CLONE DKFZP564B0769); PARTIAL CDS
BC003417	1.60	"HOMO SAPIENS, NADH DEHYDROGENASE (UBIQUINONE) 1 ALPHA SUBCOMPLEX, 10 (42KD), CLONE MGC:5103 IMAGE:3451514, MRNA, COMPLETE CDS"
NM_006601	1.60	"HOMO SAPIENS UNACTIVE PROGESTERONE RECEPTOR, 23 KD (P23), MRNA"
AF218941	1.60	"HOMO SAPIENS CLONE W39395 FORMIN 2-LIKE PROTEIN MRNA, PARTIAL CDS"
AA702323	1.60	"ZI83E03.S1 HOMO SAPIENS CDNA, 3' END"
NM_001082	1.60	"HOMO SAPIENS CYTOCHROME P450, SUBFAMILY IVF, POLYPEPTIDE 2 (CYP4F2), MRNA"
NM_017726	1.60	"HOMO SAPIENS PROTEIN PHOSPHATASE 1, REGULATORY (INHIBITOR) SUBUNIT 14D (PPP1R14D), MRNA"
AA263106	1.60	"HUMAN NUCLEIC ACID BINDING PROTEIN GENE, COMPLETE CDS."
NM_003038	1.59	"HOMO SAPIENS SOLUTE CARRIER FAMILY 1 (GLUTAMATE/NEUTRAL AMINO ACID TRANSPORTER), MEMBER 4 (SLC1A4), MRNA."
NM_030788	1.59	"HOMO SAPIENS DC-SPECIFIC TRANSMEMBRANE PROTEIN (LOC81501), MRNA"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AP000506	1.59	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 6P21.3, HLA CLASS I REGION, SECTION 5/20"
NM_025012	1.59	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ13769 (FLJ13769), MRNA"
NM_000659	1.59	"HOMO SAPIENS AUTOIMMUNE REGULATOR (AUTOIMMUNE POLYENDOCRINOPATHY CANDIDIASIS ECTODERMAL DYSTROPHY) (AIRE), TRANSCRIPT VARIANT 3, MRNA."
NM_004046	1.59	"HOMO SAPIENS ATP SYNTHASE, H+ TRANSPORTING, MITOCHONDRIAL F1 COMPLEX, ALPHA SUBUNIT, ISOFORM 1, CARDIAC MUSCLE (ATP5A1), MRNA"
NM_021905	1.59	"HOMO SAPIENS GAMMA-AMINOBUTYRIC ACID (GABA) B RECEPTOR, 1 (GABBR1), TRANSCRIPT VARIANT 4, MRNA."
NM_000054	1.59	"HOMO SAPIENS ARGININE VASOPRESSIN RECEPTOR 2 (NEPHROGENIC DIABETES INSIPIDUS) (AVPR2), MRNA."
NM_020997	1.59	"HOMO SAPIENS LEFT-RIGHT DETERMINATION, FACTOR B (LEFTB), MRNA"
NM_005044	1.59	"HOMO SAPIENS PROTEIN KINASE, X-LINKED (PRKX), MRNA."
AI807896	1.59	"HUMAN MYOSIN-IXB MRNA, COMPLETE CDS."
NM_001897	1.59	"HOMO SAPIENS CHONDROITIN SULFATE PROTEOGLYCAN 4 (MELANOMA-ASSOCIATED) (CSPG4), MRNA."
NM_013937	1.59	"HOMO SAPIENS OLFACTORY RECEPTOR, FAMILY 11, SUBFAMILY A, MEMBER 1 (OR11A1), MRNA."
NM_003830	1.59	"HOMO SAPIENS SIALIC ACID BINDING IG-LIKE LECTIN 5 (SIGLEC5), MRNA."
NM_006274	1.59	"HOMO SAPIENS SMALL INDUCIBLE CYTOKINE SUBFAMILY A (CYS-CYS), MEMBER 19 (SCYA19), MRNA."
AL049365	1.59	HOMO SAPIENS MRNA; CDNA DKFZP586A0618 (FROM CLONE DKFZP586A0618)
NM_002980	1.59	"HOMO SAPIENS SECRETIN RECEPTOR (SCTR), MRNA."
Y11710	1.59	"H.SAPIENS MRNA FOR EXTRACELLULAR MATRIX PROTEIN COLLAGEN TYPE XIV, C-TERMINUS"
AB040928	1.59	"HOMO SAPIENS MRNA FOR KIAA1495 PROTEIN, PARTIAL CDS"
BC022416	1.59	"HOMO SAPIENS, CLONE IMAGE:4243767, MRNA"
NM_001103	1.58	"HOMO SAPIENS ACTININ, ALPHA 2 (ACTN2), MRNA."
S79669	1.58	"STEROIDOGENIC ACUTE REGULATOY PROTEIN [HUMAN, FOLLICLE CELLS, MRNA, 1641 NT]"
1001739.3	1.58	NULL
Z62748	1.58	"H.SAPIENS CPG ISLAND DNA GENOMIC MSE1 FRAGMENT, CLONE 72E12, REVERSE READ CPG72E12.RT1A"
NM_001313	1.58	"HOMO SAPIENS COLLAPSIN RESPONSE MEDIATOR PROTEIN 1 (CRMP1), MRNA."
NM_000428	1.58	"HOMO SAPIENS LATENT TRANSFORMING GROWTH FACTOR BETA BINDING PROTEIN 2 (LTBP2), MRNA."
NM_020653	1.58	"HOMO SAPIENS ZINC FINGER PROTEIN 287 (ZNF287), MRNA"
NM_024301	1.58	"HOMO SAPIENS FUKUTIN-RELATED PROTEIN (FKRP), MRNA"
AK023517	1.58	"HOMO SAPIENS CDNA FLJ13455 FIS, CLONE PLACE1003256"
NM_006188	1.58	"HOMO SAPIENS ONCOMODULIN (OCM), MRNA"
BC011682	1.58	"HOMO SAPIENS, SIMILAR TO CATHEPSIN F, CLONE MGC:19716 IMAGE:3535532, MRNA, COMPLETE CDS"
AB017915	1.58	"HOMO SAPIENS MRNA FOR CHONDROITIN 6-SULFOTRANSFERASE, COMPLETE CDS"
NM_002461	1.58	"HOMO SAPIENS MEVALONATE (DIPHOSPHO) DECARBOXYLASE (MVD), MRNA."
1503660.5	1.58	NULL
BC023566	1.57	"HOMO SAPIENS, SIMILAR TO HYPOTHETICAL PROTEIN FLJ31614, CLONE MGC:20726 IMAGE:4138119, MRNA, COMPLETE CDS"
NM_016615	1.57	"HOMO SAPIENS SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, GABA), MEMBER 13 (SLC6A13), MRNA."
NM_006540	1.57	"HOMO SAPIENS NUCLEAR RECEPTOR COACTIVATOR 2 (NCOA2), MRNA."

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
U45432	1.57	"HUMAN ETV6 GENE, PROMOTER REGION AND PARTIAL CDS"
NM_014056	1.57	"HOMO SAPIENS DKFZP564K247 PROTEIN (DKFZP564K247), MRNA."
NM_014191	1.57	"HOMO SAPIENS SODIUM CHANNEL, VOLTAGE GATED, TYPE VIII, ALPHA POLYPEPTIDE (SCN8A), MRNA"
240937.12	1.57	"PROTEIN OF UNKNOWN FUNCTION, HAS HIGH SIMILARITY TO UNCHARACTERIZED MOUSE 4931408A02RIK"
X07855	1.57	"HUMAN GENE FOR ALPHA-SUBUNIT OF GI2 EXON 9, A GTP-BINDING SIGNAL TRANSDUCTION PROTEIN"
NM_001748	1.57	"HOMO SAPIENS CALPAIN 2, (M/II) LARGE SUBUNIT (CAPN2), MRNA."
NM_024492	1.57	"HOMO SAPIENS APOLIPOPROTEIN (A) RELATED GENE C (APOARGC), TRANSCRIPT VARIANT 1, MRNA"
AB023185	1.57	"HOMO SAPIENS MRNA FOR KIAA0968 PROTEIN, PARTIAL CDS"
NM_007036	1.57	"HOMO SAPIENS ENDOTHELIAL CELL-SPECIFIC MOLECULE 1 (ESM1), MRNA."
D11086	1.57	HUMAN MRNA FOR INTERLEUKIN 2 RECEPTOR GAMMA CHAIN
AB014581	1.57	"HOMO SAPIENS MRNA FOR KIAA0681 PROTEIN, PARTIAL CDS"
NM_001994	1.57	"HOMO SAPIENS COAGULATION FACTOR XIII, B POLYPEPTIDE (F13B), MRNA"
NM_018162	1.57	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10633 (FLJ10633), MRNA."
BC000429	1.57	"HOMO SAPIENS, CHROMOSOME 14 OPEN READING FRAME 2, CLONE MGC:8356 IMAGE:2819801, MRNA, COMPLETE CDS"
AF060568	1.57	"HUMAN PROMYELOCYTIC LEUKEMIA ZINC FINGER PROTEIN (PLZF) GENE, COMPLETE CDS."
NM_020980	1.57	"HOMO SAPIENS AQUAPORIN 9 (AQP9), MRNA."
S72487	1.56	"ORF1 5' TO PD-ECGF/TP...ORF2 5' TO PD-ECGF/TP [HUMAN, EPIDERMOID CARCINOMA CELL LINE A431, MRNA, 3 GENES, 1718 NT]"
NM_006934	1.56	"HOMO SAPIENS SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, GLYCINE), MEMBER 9 (SLC6A9), MRNA."
NM_006006	1.56	"HOMO SAPIENS ZINC FINGER PROTEIN 145 (KRUPPEL-LIKE, EXPRESSED IN PROMYELOCYTIC LEUKEMIA) (ZNF145), MRNA."
NM_002652	1.56	"HOMO SAPIENS PROLACTIN-INDUCED PROTEIN (PIP), MRNA."
NM_000707	1.56	"HOMO SAPIENS ARGININE VASOPRESSIN RECEPTOR 1B (AVPR1B), MRNA"
NM_000908	1.56	"HOMO SAPIENS NATRIURETIC PEPTIDE RECEPTOR C/GUANYLATE CYCLASE C (ATRIONATRIURETIC PEPTIDE RECEPTOR C) (NPR3), MRNA."
AB033096	1.56	"HOMO SAPIENS MRNA FOR KIAA1270 PROTEIN, PARTIAL CDS"
AL137558	1.56	HOMO SAPIENS MRNA; CDNA DKFZP434L1020 (FROM CLONE DKFZP434L1020)
BI759599	1.56	"603047034F1 HOMO SAPIENS CDNA, 5' END"
AK023849	1.56	"HOMO SAPIENS CDNA FLJ13787 FIS, CLONE PLACE4000670"
1116941.1	1.56	NULL
NM_019003	1.56	"HOMO SAPIENS SPINDLIN-LIKE (LOC54466), MRNA"
NM_031488	1.56	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP761I141 (DKFZP761I141), MRNA"
AB032947	1.56	"HOMO SAPIENS MRNA FOR KIAA1121 PROTEIN, PARTIAL CDS"
AF057177	1.56	HOMO SAPIENS T-CELL RECEPTOR GAMMA V1 GENE REGION
NM_007072	1.56	"HOMO SAPIENS HERV-H LTR-ASSOCIATING 2 (HHLA2), MRNA"
NM_001145	1.56	"HOMO SAPIENS ANGIOGENIN, RIBONUCLEASE, RNASE A FAMILY, 5 (ANG), MRNA."
AF287967	1.55	"HOMO SAPIENS HOMEOBOX B7 (HOXB7) GENE, PARTIAL CDS; AND HOMEOBOX B6 (HOXB6), HOMEOBOX B5 (HOXB5), HOMEOBOX B4 (HOXB4), AND HOMEOBOX B3 (HOXB3) GENES, COMPLETE CDS"
AF251237	1.55	"HOMO SAPIENS XAGE-1 MRNA, COMPLETE CDS"
1105672.1	1.55	NULL
NM_004312	1.55	"HOMO SAPIENS ARRESTIN 3, RETINAL (X-ARRESTIN) (ARR3), MRNA"
AK056198	1.55	"HOMO SAPIENS CDNA FLJ31636 FIS, CLONE NT2RI2003481"
NM_004049	1.55	"HOMO SAPIENS BCL2-RELATED PROTEIN A1 (BCL2A1), MRNA."

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_003049	1.55	"HOMO SAPIENS SOLUTE CARRIER FAMILY 10 (SODIUM/BILE ACID COTRANSPORTER FAMILY), MEMBER 1 (SLC10A1), MRNA."
NM_005122	1.55	"HOMO SAPIENS NUCLEAR RECEPTOR SUBFAMILY 1, GROUP I, MEMBER 3 (NR1I3), MRNA"
NM_014698	1.55	"HOMO SAPIENS KIAA0792 GENE PRODUCT (KIAA0792), MRNA."
AF168787	1.55	"HOMO SAPIENS VANILLOID RECEPTOR GENE, PARTIAL SEQUENCE; CARKL AND CTNS GENES, COMPLETE CDS; TIP1 GENE, PARTIAL CDS; P2X5B AND P2X5A GENES, COMPLETE CDS; AND HUMINAE GENE, PARTIAL CDS"
AP000517	1.55	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 6P21.3, HLA CLASS I REGION, SECTION 16/20"
NM_014509	1.55	"HOMO SAPIENS SERINE HYDROLASE-LIKE (SERHL), MRNA"
M96843	1.55	"HUMAN STRIATED MUSCLE CONTRACTION REGULATORY PROTEIN (ID2B) MRNA, COMPLETE CDS"
NM_003854	1.55	"HOMO SAPIENS INTERLEUKIN 1 RECEPTOR-LIKE 2 (IL1RL2), MRNA."
NM_003787	1.55	"HOMO SAPIENS NUCLEOLAR PROTEIN 4 (NOL4), MRNA."
NM_005364	1.55	"HOMO SAPIENS MELANOMA ANTIGEN, FAMILY A, 8 (MAGEA8), MRNA"
NM_021969	1.55	"HOMO SAPIENS NUCLEAR RECEPTOR SUBFAMILY 0, GROUP B, MEMBER 2 (NR0B2), MRNA."
Z83075	1.55	"H.SAPIENS FANCONI ANAEMIA GROUP A GENE, EXONS 12, 13 AND 14"
NM_000733	1.55	"HOMO SAPIENS CD3E ANTIGEN, EPSILON POLYPEPTIDE (TIT3 COMPLEX) (CD3E), MRNA."
NM_002985	1.55	"HOMO SAPIENS SMALL INDUCIBLE CYTOKINE A5 (RANTES) (SCYA5), MRNA"
NM_012306	1.55	"HOMO SAPIENS LIFEGUARD (KIAA0950), MRNA"
AF195821	1.55	"HOMO SAPIENS TNG2 (TNG2) MRNA, COMPLETE CDS"
NM_001231	1.55	"HOMO SAPIENS CALSEQUESTRIN 1 (FAST-TWITCH, SKELETAL MUSCLE) (CASQ1), NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA."
AJ414563	1.55	HOMO SAPIENS CX25 GENE FOR CONNEXIN25
AK074985	1.55	"HOMO SAPIENS CDNA FLJ90504 FIS, CLONE NT2RP3004090, WEAKLY SIMILAR TO GOLIATH PROTEIN"
NM_001056	1.54	"HOMO SAPIENS SULFOTRANSFERASE FAMILY, CYTOSOLIC, 1C, MEMBER 1 (SULT1C1), MRNA"
NM_001186	1.54	"HOMO SAPIENS BTB AND CNC HOMOLOGY 1, BASIC LEUCINE ZIPPER TRANSCRIPTION FACTOR 1 (BACH1), MRNA."
NM_000207	1.54	"HOMO SAPIENS INSULIN (INS), MRNA."
NM_006760	1.54	"HOMO SAPIENS UROPLAKIN 2 (UPK2), MRNA."
T54189	1.54	"YA92C11.R1 HOMO SAPIENS CDNA, 5' END"
AK022712	1.54	"HOMO SAPIENS CDNA FLJ12650 FIS, CLONE NT2RM4002054"
NM_018249	1.54	"HOMO SAPIENS CDK5 REGULATORY SUBUNIT ASSOCIATED PROTEIN 2 (CDK5RAP2), MRNA"
NM_015366	1.54	"HOMO SAPIENS RHO GTPASE ACTIVATING PROTEIN 8 (ARHGAP8), MRNA."
1452330.5	1.54	NULL
L25940	1.54	"HOMO SAPIENS INTEGRAL NUCLEAR ENVELOPE INNER MEMBRANE PROTEIN (LBR) GENE, EXON 11"
AA318707	1.54	"HUMAN CYSTIC FIBROSIS ANTIGEN MRNA, COMPLETE CDS."
AL137407	1.54	HOMO SAPIENS MRNA; CDNA DKFZP434M232 (FROM CLONE DKFZP434M232)
NM_002248	1.54	"HOMO SAPIENS POTASSIUM INTERMEDIATE/SMALL CONDUCTANCE CALCIUM-ACTIVATED CHANNEL, SUBFAMILY N, MEMBER 1 (KCNN1), MRNA."
NM_005544	1.54	"HOMO SAPIENS INSULIN RECEPTOR SUBSTRATE 1 (IRS1), MRNA."
AF281074	1.54	"HOMO SAPIENS NEUROPILIN 2 (NRP2) GENE, COMPLETE CDS, ALTERNATIVELY SPLICED"
AL359946	1.54	HOMO SAPIENS MRNA; CDNA DKFZP762G026 (FROM CLONE DKFZP762G026)

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AL137296	1.54	HOMO SAPIENS MRNA; CDNA DKFZP434M0416 (FROM CLONE DKFZP434M0416)
NM_001068	1.54	"HOMO SAPIENS TOPOISOMERASE (DNA) II BETA (180KD) (TOP2B), MRNA."
NM_014213	1.54	"HOMO SAPIENS HOMEO BOX D9 (HOXD9), MRNA."
NM_003392	1.54	"HOMO SAPIENS WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 5A (WNT5A), MRNA."
AA463818	1.54	ZX67D04.R1 HOMO SAPIENS CDNA 5' END
NM_032578	1.54	"HOMO SAPIENS MYOPALLADIN (FLJ14437), MRNA"
AL512713	1.54	HOMO SAPIENS MRNA; CDNA DKFZP547D086 (FROM CLONE DKFZP547D086)
NM_017707	1.54	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20199 (FLJ20199), MRNA."
NM_014217	1.54	"HOMO SAPIENS POTASSIUM CHANNEL, SUBFAMILY K, MEMBER 2 (KCNK2), MRNA"
AK025814	1.54	"HOMO SAPIENS CDNA: FLJ22161 FIS, CLONE HRC00290"
X69908	1.54	HUMAN GENE FOR MITOCHONDRIAL ATP SYNTHASE C SUBUNIT (P2 FORM).
AL163300	1.54	HOMO SAPIENS CHROMOSOME 21 SEGMENT HS21C100
NM_024895	1.53	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ23209 (FLJ23209), MRNA"
NM_058164	1.53	"HOMO SAPIENS OLFACTOMEDIN 2 (OLFM2), MRNA."
AK074293	1.53	"HOMO SAPIENS CDNA FLJ23713 FIS, CLONE HEP12771, HIGHLY SIMILAR TO GRPE PROTEIN HOMOLOG 2 PRECURSOR"
D50375	1.53	"HOMO SAPIENS MRNA FOR SILENCER ELEMENT, COMPLETE CDS"
NM_003350	1.53	"HOMO SAPIENS UBIQUITIN-CONJUGATING ENZYME E2 VARIANT 2 (UBE2V2), MRNA."
NM_024320	1.53	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC11242 (MGC11242), MRNA"
AA873020	1.53	"OA17H03.S1 HOMO SAPIENS CDNA, 3' END"
NM_004385	1.53	"HOMO SAPIENS CHONDROITIN SULFATE PROTEOGLYCAN 2 (VERSICAN) (CSPG2), MRNA."
NM_022127	1.53	"HOMO SAPIENS SOLUTE CARRIER FAMILY 28 (SODIUM-COUPLED NUCLEOSIDE TRANSPORTER), MEMBER 3 (SLC28A3), MRNA"
NM_000359	1.53	"HOMO SAPIENS TRANSGLUTAMINASE 1 (K POLYPEPTIDE EPIDERMAL TYPE I, PROTEIN-GLUTAMINE-GAMMA-GLUTAMYLTRANSFERASE) (TGM1), MRNA."
AL137616	1.53	HOMO SAPIENS MRNA; CDNA DKFZP434O1311 (FROM CLONE DKFZP434O1311)
AA297451	1.53	EST112980 HOMO SAPIENS CDNA 5' END /CLONE_END=5'
1503632.3	1.53	NULL
NM_000387	1.53	"HOMO SAPIENS SOLUTE CARRIER FAMILY 25 (CARNITINE/ACYLCARNITINE TRANSLOCASE), MEMBER 20 (SLC25A20), MITOCHONDRIAL PROTEIN ENCODED BY NUCLEAR GENE, MRNA"
AF139131	1.53	"HOMO SAPIENS BECLIN 1 (BECN1) MRNA, COMPLETE CDS"
NM_080792	1.53	"HOMO SAPIENS BRAIN-IMMUNOGLOBULIN-LIKE MOLECULE WITH TYROSINE-BASED ACTIVATION MOTIFS (BIT), MRNA"
M63391	1.53	"HUMAN DESMIN GENE, COMPLETE CDS."
D86980	1.52	"HUMAN MRNA FOR KIAA0227 GENE, PARTIAL CDS"
NM_138379	1.52	"HOMO SAPIENS HYPOTHETICAL PROTEIN BC008988 (LOC91937), MRNA"
AF217490	1.52	"HOMO SAPIENS FRAGILE 16D OXIDO REDUCTASE (FOR) GENE, EXONS 8, 9, AND PARTIAL CDS"
NM_003629	1.52	"HOMO SAPIENS PHOSPHOINOSITIDE-3-KINASE, REGULATORY SUBUNIT, POLYPEPTIDE 3 (P55, GAMMA) (PIK3R3), MRNA."
NM_052884	1.52	"HOMO SAPIENS SIALIC ACID BINDING IG-LIKE LECTIN 11 (SIGLEC11), MRNA"
AK024406	1.52	"HOMO SAPIENS CDNA FLJ14344 FIS, CLONE THYRO1001142"

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AL162066	1.52	HOMO SAPIENS MRNA; CDNA DKFZP762D096 (FROM CLONE DKFZP762D096); PARTIAL CDS
AK055539	1.52	"HOMO SAPIENS CDNA FLJ30977 FIS, CLONE HHDPC2000095, HIGHLY SIMILAR TO CRICETULUS GRISEUS LAYILIN MRNA"
NM_015425	1.52	"HOMO SAPIENS DKFZP586M0122 PROTEIN (DKFZP586M0122), MRNA."
NM_032108	1.52	"HOMO SAPIENS SEMA DOMAIN, TRANSMEMBRANE DOMAIN (TM), AND CYTOPLASMIC DOMAIN, (SEMAPHORIN) 6B (SEMA6B), MRNA."
NM_000811	1.52	"HOMO SAPIENS GAMMA-AMINOBUTYRIC ACID (GABA) A RECEPTOR, ALPHA 6 (GABRA6), MRNA"
AI718785	1.52	AS58H10.X1 HOMO SAPIENS CDNA 3' END
NM_000748	1.52	"HOMO SAPIENS CHOLINERGIC RECEPTOR, NICOTINIC, BETA POLYPEPTIDE 2 (NEURONAL) (CHRNB2), MRNA"
NM_006850	1.52	"HOMO SAPIENS INTERLEUKIN 24 (IL24), MRNA."
J05312	1.52	"HUMAN LIPOPROTEIN ASSOCIATED COAGULATION INHIBITOR (LACI) GENE, EXON 9."
NM_002588	1.52	"HOMO SAPIENS PROTOCADHERIN GAMMA SUBFAMILY C, 3 (PCDHGC3), TRANSCRIPT VARIANT 1, MRNA"
NM_031929	1.52	"HOMO SAPIENS TESTIS-SPECIFIC TRANSCRIPT, Y-LINKED 11 (TTTY11), MRNA"
AI038940	1.52	"OY86E05.X1 HOMO SAPIENS CDNA, 3' END"
NM_003482	1.52	"HOMO SAPIENS MYELOID/LYMPHOID OR MIXED-LINEAGE LEUKEMIA 2 (MLL2), MRNA"
U66047	1.52	HOMO SAPIENS CLONE Z'3-1 PLACENTA EXPRESSED MRNA FROM CHROMOSOME X
NM_014909	1.52	"HOMO SAPIENS KIAA1036 PROTEIN (KIAA1036), MRNA."
AA873769	1.52	"OI06F02.S1 NCI_CGAP_GC4 HOMO SAPIENS CDNA CLONE IMAGE:1475739 3', MRNA SEQUENCE"
AA037140	1.52	"ZC53F10.R1 HOMO SAPIENS CDNA, 5' END"
NM_006365	1.52	"HOMO SAPIENS TRANSCRIPTIONAL ACTIVATOR OF THE C-FOS PROMOTER (CROC4), MRNA"
NM_003803	1.52	"HOMO SAPIENS MYOMESIN 1 (SKELEMIN) (185KD) (MYOM1), MRNA."
AB023151	1.52	"HOMO SAPIENS MRNA FOR KIAA0934 PROTEIN, PARTIAL CDS"
NM_006662	1.52	"HOMO SAPIENS SNF2-RELATED CBP ACTIVATOR PROTEIN (SRCAP), MRNA."
NM_032369	1.52	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC15619 (MGC15619), MRNA"
AL163259	1.52	NULL
NM_000836	1.52	"HOMO SAPIENS GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL D-ASPARTATE 2D (GRIN2D), MRNA"
M10014	1.51	HUMAN FIBRINOGEN GENE (FGG).
NM_017618	1.51	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20006 (FLJ20006), MRNA"
AB009076	1.51	"HOMO SAPIENS GENE FOR COMPLEMENT C1S, PARTIAL CDS"
AF118081	1.51	"HOMO SAPIENS PRO1900 MRNA, COMPLETE CDS"
NM_004694	1.51	"HOMO SAPIENS SOLUTE CARRIER FAMILY 16 (MONOCARBOXYLIC ACID TRANSPORTERS), MEMBER 6 (SLC16A6), MRNA."
AI052482	1.51	"OZ19F08.X1 HOMO SAPIENS CDNA, 3' END"
887776.1	1.51	"PROTEIN WITH VERY STRONG SIMILARITY TO ALBUMIN (RAT ALB), WHICH IS A BLOOD PLASMA PROTEIN, HUMAN ALB IS ASSOCIATED WITH FAMILIAL DYSALBUMINEMIC HYPERTHYROXINEMIA AND ANALBUMINEMIA, MEMBER OF THE SERUM ALBUMIN FAMILY"
AF313465	1.51	"HOMO SAPIENS SODIUM BICARBONATE COTRANSPORTER (SLC4A9) MRNA, PARTIAL CDS"
M17285	1.51	HUMAN INSULIN-LIKE GROWTH FACTOR (IGF-II) GENE
M87708	1.51	HUMAN SIMPLE REPEAT POLYMORPHISM
NM_080739	1.51	"HOMO SAPIENS CHROMOSOME 20 OPEN READING FRAME 141 (C20ORF141), MRNA."
NM_032621	1.51	"HOMO SAPIENS X-LINKED PROTEIN (DJ79P11.1), MRNA."

APPENDIX 2

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_005425	1.51	"HOMO SAPIENS TRANSITION PROTEIN 2 (DURING HISTONE TO PROTAMINE REPLACEMENT) (TNP2), MRNA."
NM_007017	1.51	"HOMO SAPIENS SRY (SEX DETERMINING REGION Y)-BOX 30 (SOX30), MRNA."
NM_000340	1.51	"HOMO SAPIENS SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 2 (SLC2A2), MRNA."
NM_018652	1.51	"HOMO SAPIENS GOLGIN-LIKE PROTEIN (GLP), MRNA"
NM_031275	1.51	"HOMO SAPIENS TESTIS EXPRESSED SEQUENCE 12 (TEX12), MRNA"
NM_002650	1.51	"HOMO SAPIENS PHOSPHATIDYLINOSITOL 4-KINASE, CATALYTIC, ALPHA POLYPEPTIDE (PIK4CA), TRANSCRIPT VARIANT 1, MRNA."
NM_006258	1.51	"HOMO SAPIENS PROTEIN KINASE, CGMP-DEPENDENT, TYPE I (PRKG1), MRNA."
AB020671	1.51	"HOMO SAPIENS MRNA FOR KIAA0864 PROTEIN, PARTIAL CDS"
NM_024787	1.51	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12526 (FLJ12526), MRNA"
AF055378	1.51	"HOMO SAPIENS LONG FORM TRANSCRIPTION FACTOR C-MAF (C-MAF) GENE, EXON 2 AND PARTIAL CDS"
BC001427	1.51	"HOMO SAPIENS, HYPOTHETICAL PROTEIN FLJ11320, CLONE MGC:894 IMAGE:3139599, MRNA, COMPLETE CDS"
NM_022803	1.51	"HOMO SAPIENS UNCOUPLING PROTEIN 3 (MITOCHONDRIAL, PROTON CARRIER) (UCP3), TRANSCRIPT VARIANT SHORT, NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA."
NM_016944	1.51	"HOMO SAPIENS TASTE RECEPTOR, TYPE 2, MEMBER 4 (TAS2R4), MRNA"
L44140	1.51	"HUMAN CHROMOSOME X REGION FROM FILAMIN (FLN) GENE TO GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) GENE, COMPLETE CDS'S."
AB046814	1.51	"HOMO SAPIENS MRNA FOR KIAA1594 PROTEIN, PARTIAL CDS"
AK000694	1.50	"HOMO SAPIENS CDNA FLJ20687 FIS, CLONE KAIA302, HIGHLY SIMILAR TO AF039702 HOMO SAPIENS ANTIGEN NY-CO-43 MRNA"
AK024999	1.50	"HOMO SAPIENS CDNA: FLJ21346 FIS, CLONE COL02705"
NM_003212	1.50	"HOMO SAPIENS TERATOCARCINOMA-DERIVED GROWTH FACTOR 1 (TDGF1), MRNA"
NM_014634	1.50	"HOMO SAPIENS KIAA0015 GENE PRODUCT (KIAA0015), MRNA."
AP000497	1.50	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 3P21.3, CLONE:301 TO 308, ANTI-ONCOGENE REGION, SECTION 5/5"
NM_020482	1.50	"HOMO SAPIENS ACTIVATOR OF CAMP-RESPONSIVE ELEMENT MODULATOR (CREM) IN TESTIS (ACT), MRNA"
NM_001330	1.50	"HOMO SAPIENS CARDIOTROPHIN 1 (CTF1), MRNA."
NM_005275	1.50	"HOMO SAPIENS GUANINE NUCLEOTIDE BINDING PROTEIN-LIKE 1 (GNL1), MRNA"

Appendix 3

Down Regulated Genes with Treatment Fex:		
Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_006984	0.13	"HOMO SAPIENS CLAUDIN 10 (CLDN10), MRNA"
NM_000710	0.17	"HOMO SAPIENS BRADYKININ RECEPTOR B1 (BDKRB1), MRNA"
NM_031958	0.20	"HOMO SAPIENS KERATIN ASSOCIATED PROTEIN 3.1 (KRTAP3.1), MRNA"
475365.6	0.21	"MEMBER OF THE CARBOXYPEPTIDASE A METALLOPROTEASE (M14) FAMILY OF ZINC CARBOXYPEPTIDASES, HAS MODERATE SIMILARITY TO CARBOXYPEPTIDASE B2 (MOUSE CPB2), WHICH IS A PLASMA PRO-FORM METALLOPROTEASE THAT IS AN ACUTE PHASE PROTEIN UPREGULATED IN INFLAMMATION"
AK026959	0.23	"HOMO SAPIENS CDNA: FLJ23306 FIS, CLONE HEP11541"
NM_030572	0.23	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC10946 (MGC10946), MRNA"
NM_004407	0.24	"HOMO SAPIENS DENTIN MATRIX ACIDIC PHOSPHOPROTEIN (DMP1), MRNA"
NM_018436	0.25	"HOMO SAPIENS ALLANTOICASE (ALLC), MRNA"
NM_003102	0.26	"HOMO SAPIENS SUPEROXIDE DISMUTASE 3, EXTRACELLULAR (SOD3), MRNA"
NM_004575	0.26	"HOMO SAPIENS POU DOMAIN, CLASS 4, TRANSCRIPTION FACTOR 2 (POU4F2), MRNA"
D28113	0.26	"HUMAN MRNA FOR MOBP (MYELIN-ASSOCIATED OLIGODENDROCYTIC BASIC PROTEIN), COMPLETE CDS, CLONE HOPRP1"
NM_144658	0.28	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ32122 (FLJ32122), MRNA"
NM_000584	0.29	"HOMO SAPIENS INTERLEUKIN 8 (IL8), MRNA."
NM_024687	0.30	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ23049 (FLJ23049), MRNA"
NM_014391	0.31	"HOMO SAPIENS CARDIAC ANKYRIN REPEAT PROTEIN (CARP), MRNA"
Z60717	0.31	"H.SAPIENS CPG ISLAND DNA GENOMIC MSE1 FRAGMENT, CLONE 33A10, FORWARD READ CPG33A10.FT1I"
NM_024340	0.32	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC4179 (MGC4179), MRNA"
D86425	0.32	"HOMO SAPIENS MRNA FOR OSTEONIDOGEN, COMPLETE CDS"
AL122109	0.33	HOMO SAPIENS MRNA; CDNA DKFZP434M1827 (FROM CLONE DKFZP434M1827)
NM_024306	0.33	"HOMO SAPIENS FATTY ACID HYDROXYLASE (FAAH), MRNA"
AF043195	0.34	"HOMO SAPIENS TIGHT JUNCTION PROTEIN ZO-2 (TJP2) GENE, ALTERNATIVE PROMOTER PA AND EXON A"
NM_002089	0.35	"HOMO SAPIENS GRO2 ONCOGENE (GRO2), MRNA."
NM_018679	0.35	"HOMO SAPIENS T-COMPLEX 11 (MOUSE) (TCP11), MRNA"
NM_003311	0.35	"HOMO SAPIENS TUMOR SUPPRESSING SUBTRANSFERABLE CANDIDATE 3 (TSSC3), MRNA."
NM_014890	0.36	"HOMO SAPIENS DOWNREGULATED IN OVARIAN CANCER 1 (DOC1), MRNA."
NM_032883	0.36	"HOMO SAPIENS CHROMOSOME 20 OPEN READING FRAME 100 (C20ORF100), MRNA"
NM_005925	0.36	"HOMO SAPIENS MEPRIN A, BETA (MEP1B), MRNA"
BC000623	0.37	"HOMO SAPIENS, SIMILAR TO HYPOTHETICAL PROTEIN FLJ20211, CLONE MGC:1068 IMAGE:3346325, MRNA, COMPLETE CDS"
180648.1	0.37	PROTEIN CONTAINING FIVE MORN (MEMBRANE OCCUPATION AND RECOGNITION NEXUS) REPEATS
NM_032263	0.38	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP434B227 (DKFZP434B227), MRNA"
AK023937	0.38	"HOMO SAPIENS CDNA FLJ13875 FIS, CLONE THYRO1001374, WEAKLY SIMILAR TO CYTOSOLIC ACYL COENZYME A THIOESTER HYDROLASE (EC 3.1.2.2)"
AK026071	0.38	"HOMO SAPIENS CDNA: FLJ22418 FIS, CLONE HRC08590"
D55641	0.39	"HUMAN SKIN FIBROBLAST PABL (PSEUDOAUTOSOMAL BOUNDARY-LIKE SEQUENCE) MRNA, CLONE SK13"
BF692587	0.39	602248939F1 HOMO SAPIENS CDNA 5' END
AF168681	0.39	"HOMO SAPIENS CRIM1 PROTEIN GENE, PARTIAL CDS; AND FEZ2 GENE, PARTIAL SEQUENCE"
AL046937	0.40	DKFZP586I2417_R1 HOMO SAPIENS CDNA 5' END
NM_014331	0.40	"HOMO SAPIENS SOLUTE CARRIER FAMILY 7, (CATIONIC AMINO ACID TRANSPORTER, Y+ SYSTEM) MEMBER 11 (SLC7A11), MRNA"
NM_012275	0.41	"HOMO SAPIENS INTERLEUKIN 1 FAMILY, MEMBER 5 (DELTA) (IL1F5), MRNA"
NM_015003	0.42	"HOMO SAPIENS GOLGIN-67 (KIAA0855), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
U09197	0.42	HUMAN 5.5 KB MRNA UPREGULATED IN RETINOIC ACID TREATED HL-60 NEUTROPHILIC CELLS
AL137477	0.42	HOMO SAPIENS MRNA; CDNA DKFZP434K2323 (FROM CLONE DKFZP434K2323); PARTIAL CDS
NM_006516	0.42	"HOMO SAPIENS SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1 (SLC2A1), MRNA."
AI435998	0.42	"TH80E05.X1 HOMO SAPIENS CDNA, 3' END"
AL050169	0.42	HOMO SAPIENS MRNA; CDNA DKFZP586D0922 (FROM CLONE DKFZP586D0922)
NM_006279	0.42	"HOMO SAPIENS SIALYLTRANSFERASE 6 (N-ACETYLLACOSAMINIDE ALPHA 2,3-SIALYLTRANSFERASE) (SIAT6), MRNA."
NM_006163	0.42	"HOMO SAPIENS NUCLEAR FACTOR (ERYTHROID-DERIVED 2), 45KD (NFE2), MRNA."
BC035810	0.43	"HOMO SAPIENS, CLONE IMAGE:5754421, MRNA, PARTIAL CDS"
AK026485	0.43	"HOMO SAPIENS CDNA: FLJ22832 FIS, CLONE KAIA4195"
NM_017911	0.43	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20635 (FLJ20635), MRNA"
L40326	0.43	"HOMO SAPIENS HEPATITIS B VIRUS X-ASSOCIATED PROTEIN 1 MRNA, COMPLETE CDS"
AK000819	0.44	"HOMO SAPIENS CDNA FLJ20812 FIS, CLONE ADSE01316"
NM_002423	0.44	"HOMO SAPIENS MATRIX METALLOPROTEINASE 7 (MATRILYSIN, UTERINE) (MMP7), MRNA."
AK097430	0.44	"HOMO SAPIENS CDNA FLJ40111 FIS, CLONE TESTI2008320, MODERATELY SIMILAR TO HOMO SAPIENS MITOGEN-ACTIVATED PROTEIN KINASE PHOSPHATASE X (MKPX) MRNA"
NM_015515	0.45	"HOMO SAPIENS TYPE I INTERMEDIATE FILAMENT CYTOKERATIN (HAIK1), MRNA."
NM_139215	0.45	"HOMO SAPIENS TAF15 RNA POLYMERASE II, TATA BOX BINDING PROTEIN (TBP)-ASSOCIATED FACTOR, 68 KD (TAF15), TRANSCRIPT VARIANT 1, MRNA"
NM_003025	0.45	"HOMO SAPIENS SH3-DOMAIN GRB2-LIKE 1 (SH3GL1), MRNA."
BC007008	0.45	"HOMO SAPIENS, CRYSTALLIN, ALPHA B, CLONE MGC:12326 IMAGE:3933748, MRNA, COMPLETE CDS"
NM_005195	0.46	"HOMO SAPIENS CCAAT/ENHANCER BINDING PROTEIN (C/EBP), DELTA (CEBPD), MRNA."
NM_004591	0.46	"HOMO SAPIENS SMALL INDUCIBLE CYTOKINE SUBFAMILY A (CYS-CYS), MEMBER 20 (SCYA20), MRNA"
AK024998	0.46	"HOMO SAPIENS CDNA: FLJ21345 FIS, CLONE COL02694"
NM_017773	0.47	"HUMAN DEFENSIN 6 MRNA, COMPLETE CDS."
AP000505	0.47	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 6P21.3, HLA CLASS I REGION, SECTION 4/20"
NM_012206	0.47	"HOMO SAPIENS HEPATITIS A VIRUS CELLULAR RECEPTOR 1 (HAVCR-1), MRNA."
NM_016218	0.47	"HOMO SAPIENS POLYMERASE (DNA-DIRECTED) KAPPA (POLK), MRNA"
NM_021634	0.47	"HOMO SAPIENS LEUCINE-RICH REPEAT-CONTAINING G PROTEIN-COUPLED RECEPTOR 7 (LGR7), MRNA"
AB032969	0.47	"HOMO SAPIENS MRNA FOR KIAA1143 PROTEIN, PARTIAL CDS"
NM_005354	0.47	"HOMO SAPIENS JUN D PROTO-ONCOGENE (JUND), MRNA."
NM_001554	0.48	"HOMO SAPIENS CYSTEINE-RICH, ANGIOGENIC INDUCER, 61 (CYR61), MRNA"
NM_000928	0.48	"HOMO SAPIENS PHOSPHOLIPASE A2, GROUP IB (PANCREAS) (PLA2G1B), NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA"
NM_017736	0.48	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20274 (FLJ20274), MRNA"
M37457	0.48	"HUMAN NA+,K+ -ATPASE CATALYTIC SUBUNIT ALPHA-III ISOFORM GENE, EXON 23, CLONE LAMBDA-NK-ALPHA-R3-2"
NM_000530	0.49	"HOMO SAPIENS MYELIN PROTEIN ZERO (CHARCOT-MARIE-TOOTH NEUROPATHY 1B) (MPZ), MRNA"
D43639	0.49	"HUMAN GENE FOR PREPROADRENOMEDULLIN, COMPLETE CDS (EXON 1-4)"
NM_005420	0.49	"HOMO SAPIENS SULFOTRANSFERASE, ESTROGEN-PREFERRING (STE), MRNA."
NM_032837	0.49	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ14775 (FLJ14775), MRNA"
203751.1	0.49	PROTEIN OF UNKNOWN FUNCTION
NM_021101	0.49	"HOMO SAPIENS CLAUDIN 1 (CLDN1), MRNA."
NM_024889	0.49	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ23537 (FLJ23537), MRNA"
NM_022133	0.49	"HOMO SAPIENS SORTING NEXIN 16 (SNX16), MRNA"
AB011128	0.49	"HOMO SAPIENS MRNA FOR KIAA0556 PROTEIN, PARTIAL CDS"
AK090409	0.49	HOMO SAPIENS MRNA FOR FLJ00300 PROTEIN

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_022122	0.49	"HOMO SAPIENS MATRIX METALLOPROTEINASE 27 (MMP27), MRNA"
NM_001300	0.50	"HOMO SAPIENS CORE PROMOTER ELEMENT BINDING PROTEIN (COPEB), MRNA"
NM_003557	0.50	"HOMO SAPIENS PHOSPHATIDYLINOSITOL-4-PHOSPHATE 5-KINASE, TYPE I, ALPHA (PIP5K1A), MRNA."
AB037779	0.50	"HOMO SAPIENS MRNA FOR KIAA1358 PROTEIN, PARTIAL CDS"
NM_004420	0.50	"HOMO SAPIENS DUAL SPECIFICITY PHOSPHATASE 8 (DUSP8), MRNA."
NM_005627	0.50	"HOMO SAPIENS SERUM/GLUCOCORTICOID REGULATED KINASE (SGK), MRNA."
1168293.1	0.50	NULL
AB007892	0.50	"HOMO SAPIENS KIAA0432 MRNA, COMPLETE CDS"
NM_016140	0.50	"HOMO SAPIENS BRAIN SPECIFIC PROTEIN (LOC51673), MRNA."
NM_012342	0.50	"HOMO SAPIENS PUTATIVE TRANSMEMBRANE PROTEIN (NMA), MRNA."
NM_001086	0.50	"HOMO SAPIENS ARYLACETAMIDE DEACETYLASE (ESTERASE) (AADAC), MRNA."
1345454.1	0.50	NULL
NM_033344	0.50	"HOMO SAPIENS EGL NINE HOMOLOG 3 (C. ELEGANS) (EGLN3), MRNA."
NM_003113	0.51	"HOMO SAPIENS NUCLEAR ANTIGEN SP100 (SP100), MRNA"
BC015134	0.51	"HOMO SAPIENS, CLONE IMAGE:3934391, MRNA"
NM_002260	0.51	"HOMO SAPIENS KILLER CELL LECTIN-LIKE RECEPTOR SUBFAMILY C, MEMBER 2 (KLRC2), MRNA."
AK097698	0.51	"HOMO SAPIENS CDNA FLJ40379 FIS, CLONE TESTI2035262, WEAKLY SIMILAR TO PROACTIVATOR POLYPEPTIDE PRECURSOR"
BC004982	0.51	"HOMO SAPIENS, GLUCOSE PHOSPHATE ISOMERASE, CLONE MGC:3935 IMAGE:2906270, MRNA, COMPLETE CDS"
NM_001629	0.51	"HOMO SAPIENS ARACHIDONATE 5-LIPOXYGENASE-ACTIVATING PROTEIN (ALOX5AP), MRNA."
NM_023068	0.51	"HOMO SAPIENS SIALOADHESIN (SN), MRNA"
NM_005978	0.52	"HOMO SAPIENS S100 CALCIUM BINDING PROTEIN A2 (S100A2), MRNA."
Z72499	0.52	H.SAPIENS MRNA FOR HERPESVIRUS ASSOCIATED UBIQUITIN-SPECIFIC PROTEASE (HAUSP)
AP003355	0.52	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 8Q23, CLONE: KB1517D11"
NM_033260	0.52	"HOMO SAPIENS WINGED HELIX/FORKHEAD TRANSCRIPTION FACTOR (HFH1), MRNA"
NM_001901	0.52	"HOMO SAPIENS CONNECTIVE TISSUE GROWTH FACTOR (CTGF), MRNA."
NM_001562	0.52	"HOMO SAPIENS INTERLEUKIN 18 (INTERFERON-GAMMA-INDUCING FACTOR) (IL18), MRNA."
1401176.1	0.52	NULL
AJ420585	0.52	HOMO SAPIENS MRNA FULL LENGTH INSERT CDNA CLONE EUROIMAGE 1964662
BG752423	0.52	"602730910F1 NIH_MGC_43 HOMO SAPIENS CDNA CLONE IMAGE:4874427 5', MRNA SEQUENCE"
BC008810	0.52	"HOMO SAPIENS, CLONE IMAGE:3948909, MRNA, PARTIAL CDS"
NM_020299	0.52	"HOMO SAPIENS ALDO-KETO REDUCTASE FAMILY 1, MEMBER B10 (ALDOSE REDUCTASE) (AKR1B10), MRNA."
NM_003358	0.52	"HOMO SAPIENS UDP-GLUCOSE CERAMIDE GLUCOSYLTRANSFERASE (UGCG), MRNA."
M80478	0.52	"HUMAN PLATELET GLYCOPROTEIN IX PRECURSOR (GPIX) GENE, COMPLETE CDS"
NM_001657	0.53	"HOMO SAPIENS AMPHIREGULIN (SCHWANNOMA-DERIVED GROWTH FACTOR) (AREG), MRNA."
NM_003212	0.53	"HOMO SAPIENS TERATOCARCINOMA-DERIVED GROWTH FACTOR 1 (TDGF1), MRNA."
NM_024325	0.53	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC10715 (MGC10715), MRNA"
NM_005242	0.53	"HOMO SAPIENS COAGULATION FACTOR II (THROMBIN) RECEPTOR-LIKE 1 (F2RL1), MRNA"
NM_005797	0.53	"HOMO SAPIENS EPITHELIAL V-LIKE ANTIGEN 1 (EVA1), MRNA."
NM_001348	0.53	"HOMO SAPIENS DEATH-ASSOCIATED PROTEIN KINASE 3 (DAPK3), MRNA."
NM_024501	0.53	"HOMO SAPIENS HOMEO BOX D1 (HOXD1), MRNA"
NM_004864	0.53	"HOMO SAPIENS PROSTATE DIFFERENTIATION FACTOR (PLAB), MRNA"
AF016903	0.53	"HOMO SAPIENS AGRIN PRECURSOR MRNA, PARTIAL CDS"
NM_152908	0.53	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ31196 (FLJ31196), MRNA"
NM_006753	0.54	"HOMO SAPIENS SURFEIT 6 (SURF6), MRNA"
NM_017654	0.54	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20073 (FLJ20073), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_001165	0.54	"HOMO SAPIENS BACULOVIRAL IAP REPEAT-CONTAINING 3 (BIRC3), MRNA."
NM_016639	0.54	"HOMO SAPIENS TYPE I TRANSMEMBRANE PROTEIN FN14 (FN14), MRNA."
AL162045	0.54	HOMO SAPIENS MRNA; CDNA DKFZP761P0212 (FROM CLONE DKFZP761P0212); PARTIAL CDS
AK026784	0.54	"HOMO SAPIENS CDNA: FLJ23131 FIS, CLONE LNG08502"
NM_145298	0.54	"HOMO SAPIENS SIMILAR TO PHORBOLIN 3 (APOBEC1-LIKE) (LOC200316), MRNA"
BG546997	0.54	602573989F1 HOMO SAPIENS CDNA 5' END
NM_017651	0.54	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20069 (FLJ20069), MRNA"
NM_001346	0.54	"HOMO SAPIENS DIACYLGLYCEROL KINASE, GAMMA (90KD) (DGKG), MRNA."
NM_030587	0.54	"HOMO SAPIENS UDP-GAL:BETAGLCNAC BETA 1,4-GALACTOSYLTRANSFERASE, POLYPEPTIDE 2 (B4GALT2), TRANSCRIPT VARIANT 1, MRNA."
NM_024796	0.54	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ22639 (FLJ22639), MRNA"
NM_015720	0.54	"HOMO SAPIENS ENDOGLYCAN (PODLX2), MRNA."
AK023317	0.54	"HOMO SAPIENS CDNA FLJ13255 FIS, CLONE OVARC1000800, MODERATELY SIMILAR TO MITOCHONDRIAL STRESS-70 PROTEIN PRECURSOR"
NM_006901	0.54	"HOMO SAPIENS MYOSIN IXA (MYO9A), MRNA."
NM_001553	0.55	"HOMO SAPIENS INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN 7 (IGFBP7), MRNA"
M80899	0.55	"HUMAN NOVEL PROTEIN AHNAK MRNA, PARTIAL SEQUENCE"
NM_002658	0.55	"HOMO SAPIENS PLASMINOGEN ACTIVATOR, UROKINASE (PLAU), MRNA."
NM_012227	0.55	"HOMO SAPIENS PSEUDOAUTOSOMAL GTP-BINDING PROTEIN-LIKE (PGPL), MRNA."
NM_022783	0.55	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12428 (FLJ12428), MRNA."
AK024489	0.55	"HOMO SAPIENS MRNA FOR FLJ00089 PROTEIN, PARTIAL CDS"
NM_002228	0.55	"HOMO SAPIENS V-JUN SARCOMA VIRUS 17 ONCOGENE HOMOLOG (AVIAN) (JUN), MRNA."
NM_000683	0.55	"HOMO SAPIENS ADRENERGIC, ALPHA-2C-, RECEPTOR (ADRA2C), MRNA."
AL136680	0.55	HOMO SAPIENS MRNA; CDNA DKFZP564C2478 (FROM CLONE DKFZP564C2478); COMPLETE CDS
NM_006931	0.55	"HOMO SAPIENS SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 3 (SLC2A3), MRNA."
NM_019096	0.55	"HOMO SAPIENS GTP BINDING PROTEIN 2 (GTPBP2), MRNA."
AF218032	0.55	HOMO SAPIENS CLONE PP902 UNKNOWN MRNA
NM_002648	0.55	"HOMO SAPIENS PIM-1 ONCOGENE (PIM1), MRNA."
NM_002892	0.55	"HOMO SAPIENS RETINOBLASTOMA BINDING PROTEIN 1 (RBBP1), TRANSCRIPT VARIANT 1, MRNA"
NM_032119	0.55	"HOMO SAPIENS VERY LARGE G PROTEIN-COUPLED RECEPTOR 1 (VLGR1), MRNA"
NM_024606	0.55	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ11756 (FLJ11756), MRNA."
NM_003082	0.56	"HOMO SAPIENS SMALL NUCLEAR RNA ACTIVATING COMPLEX, POLYPEPTIDE 1, 43KD (SNAPC1), MRNA."
NM_022837	0.56	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ22833 (FLJ22833), MRNA"
NM_025043	0.56	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ22404 (FLJ22404), MRNA"
NM_004468	0.56	"HOMO SAPIENS FOUR AND A HALF LIM DOMAINS 3 (FHL3), MRNA."
L19314	0.56	"HUMAN HRY GENE, COMPLETE CDS"
AL119114	0.56	"DKFZP761H1212_S1 HOMO SAPIENS CDNA, 3' END"
NM_001453	0.56	"HOMO SAPIENS FORKHEAD BOX C1 (FOXC1), MRNA"
NM_000354	0.56	"HOMO SAPIENS SERINE (OR CYSTEINE) PROTEINASE INHIBITOR, CLADE A (ALPHA-1 ANTIPROTEINASE, ANTITRYPSIN), MEMBER 7 (SERPINA7), MRNA"
X03069	0.56	HUMAN MRNA FOR HLA-D CLASS II ANTIGEN DR1 BETA CHAIN
NM_152901	0.56	"HOMO SAPIENS PYRIN-DOMAIN CONTAINING PROTEIN 1 (PYC1), MRNA"
NM_012242	0.56	"HOMO SAPIENS DICKKOPF HOMOLOG 1 (XENOPUS LAEVIS) (DKK1), MRNA."
NM_033445	0.56	"HOMO SAPIENS SIMILAR TO H2A HISTONE FAMILY, MEMBER A (H. SAPIENS) (MGC3165), MRNA"
X70287	0.56	"H.SAPIENS GENE FOR THIOREDOXIN, EXONS 2 AND 3"
NM_018177	0.56	"HOMO SAPIENS NEDD4 BINDING PROTEIN 2 (N4BP2), MRNA"
AL390142	0.56	HOMO SAPIENS MRNA; CDNA DKFZP547N024 (FROM CLONE DKFZP547N024)
AB038689	0.56	"HOMO SAPIENS AHSG GENE FOR ALPHA2-HS GLYCOPROTEIN, COMPLETE CDS"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_017878	0.56	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20552 (FLJ20552), MRNA."
AL834442	0.56	HOMO SAPIENS MRNA; CDNA DKFZP761B2210 (FROM CLONE DKFZP761B2210)
NG_001068	0.56	"HOMO SAPIENS ACTIN, GAMMA PSEUDOGENE 1 (ACTGP1) ON CHROMOSOME 3"
NM_012267	0.56	"HOMO SAPIENS HSP70-INTERACTING PROTEIN (HSPBP1), MRNA."
NM_024114	0.57	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC4827 (MGC4827), MRNA"
NM_000337	0.57	"HOMO SAPIENS SARCOGLYCAN, DELTA (35KD DYSTROPHIN-ASSOCIATED GLYCOPROTEIN) (SGCD), MRNA"
NM_018929	0.57	"HOMO SAPIENS PROTOCADHERIN GAMMA SUBFAMILY C, 5 (PCDHGC5), TRANSCRIPT VARIANT 1, MRNA"
NM_015363	0.57	"HOMO SAPIENS ZINC FINGER, IMPRINTED 2 (ZIM2), MRNA"
NM_004064	0.57	"HOMO SAPIENS CYCLIN-DEPENDENT KINASE INHIBITOR 1B (P27, KIP1) (CDKN1B), MRNA"
NM_015894	0.57	"HOMO SAPIENS STATHMIN-LIKE 3 (STMN3), MRNA."
NM_014810	0.57	"HOMO SAPIENS KIAA0480 GENE PRODUCT (KIAA0480), MRNA."
NM_005035	0.57	"HOMO SAPIENS POLYMERASE (RNA) MITOCHONDRIAL (DNA DIRECTED) (POLRMT), NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA"
475198.1	0.57	"PROTEIN WITH HIGH SIMILARITY TO RAT RINZF, WHICH BINDS A RAT GAS REGULATORY ELEMENT IMPORTANT FOR PANCREAS INSULINOMA-SPECIFIC EXPRESSION, CONTAINS TWO C2H2 TYPE ZINC FINGER DOMAINS AND A BTB (BR-C, TTK AND BABOR) OR POZ (POX VIRUS AND ZINC FINGER) DOMAI
NM_017958	0.57	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20783 (FLJ20783), MRNA."
AB051492	0.57	"HOMO SAPIENS MRNA FOR KIAA1705 PROTEIN, PARTIAL CDS"
NM_032624	0.57	"HOMO SAPIENS HYPOTHETICAL BRAIN PROTEIN MY050 (MY050), MRNA"
NM_002307	0.57	"HOMO SAPIENS LECTIN, GALACTOSIDE-BINDING, SOLUBLE, 7 (GALECTIN 7) (LGALS7), MRNA."
NM_002333	0.57	"HOMO SAPIENS LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 3 (LRP3), MRNA."
AK027843	0.57	"HOMO SAPIENS CDNA FLJ14937 FIS, CLONE PLACE1010231, WEAKLY SIMILAR TO CELL SURFACE GLYCOPROTEIN EMR1 PRECURSOR"
NM_006623	0.57	"HOMO SAPIENS PHOSPHOGLYCERATE DEHYDROGENASE (PHGDH), MRNA"
NM_024765	0.57	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12401 (FLJ12401), MRNA"
AF181897	0.58	"HOMO SAPIENS WRN (WRN) GENE, COMPLETE CDS"
1330303.1	0.58	NULL
NM_139314	0.58	"HOMO SAPIENS ANGIOPOIETIN-LIKE 4 (ANGPTL4), TRANSCRIPT VARIANT 1, MRNA"
M25295	0.58	"HUMAN KERATINOCYTE GROWTH FACTOR MRNA, COMPLETE CDS"
NM_001550	0.58	"HOMO SAPIENS INTERFERON-RELATED DEVELOPMENTAL REGULATOR 1 (IFRD1), MRNA"
NM_014059	0.58	"HOMO SAPIENS RGC32 PROTEIN (RGC32), MRNA"
NM_018017	0.58	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10188 (FLJ10188), MRNA."
NM_020130	0.58	"HOMO SAPIENS CHROMOSOME 8 OPEN READING FRAME 4 (C8ORF4), MRNA"
NM_002856	0.58	"HOMO SAPIENS POLIOVIRUS RECEPTOR-RELATED 2 (HERPESVIRUS ENTRY MEDIATOR B) (PVRL2), MRNA."
J02853	0.58	"HOMO SAPIENS CASEIN KINASE II ALPHA SUBUNIT MRNA, COMPLETE CDS"
NM_018364	0.58	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ11220 (FLJ11220), MRNA"
NM_000670	0.58	"HOMO SAPIENS ALCOHOL DEHYDROGENASE 4 (CLASS II), PI POLYPEPTIDE (ADH4), MRNA."
AK095284	0.58	"HOMO SAPIENS CDNA FLJ37965 FIS, CLONE CTONG2009844"
U65404	0.58	"HUMAN ERYTHROID-SPECIFIC TRANSCRIPTION FACTOR EKLF MRNA, COMPLETE CDS"
NM_004269	0.58	"HOMO SAPIENS COFACTOR REQUIRED FOR SP1 TRANSCRIPTIONAL ACTIVATION, SUBUNIT 8 (34KD) (CRSP8), MRNA."
NM_018231	0.58	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10815 (FLJ10815), MRNA."
AF070443	0.58	"HOMO SAPIENS GLCNAC-1-P TRANSFERASE GENE, EXONS 5 THROUGH 9 AND COMPLETE CDS"
NM_024679	0.58	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ11939 (FLJ11939), MRNA"
NM_000422	0.58	"HOMO SAPIENS KERATIN 17 (KRT17), MRNA"
AF274889	0.58	"HOMO SAPIENS GLUCOSE TRANSPORTER 3 GENE, EXONS 1 TO 6"
NM_052830	0.58	"HOMO SAPIENS GAMMA-GLUTAMYLTRANSFERASE-LIKE 3 (GGTL3), MRNA"
1330160.23	0.58	PROTEIN OF UNKNOWN FUNCTION

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
403813.2	0.58	PROTEIN OF UNKNOWN FUNCTION
NM_020921	0.58	"HOMO SAPIENS NINEIN (GSK3B INTERACTING PROTEIN) (NIN), MRNA"
NM_024067	0.58	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC2718 (MGC2718), MRNA"
NM_016210	0.59	"HOMO SAPIENS G20 PROTEIN (LOC51161), MRNA."
BC008357	0.59	"HOMO SAPIENS, CLONE IMAGE:3605655, MRNA"
NM_006086	0.59	"HOMO SAPIENS TUBULIN, BETA, 4 (TUBB4), MRNA."
NM_014502	0.59	"HOMO SAPIENS NUCLEAR MATRIX PROTEIN NMP200 RELATED TO SPLICING FACTOR PRP19 (NMP200), MRNA."
NM_001614	0.59	"HOMO SAPIENS ACTIN, GAMMA 1 (ACTG1), MRNA"
NM_030753	0.59	"HOMO SAPIENS WINGLESS-TYPE MMTV INTEGRATION SITE FAMILY, MEMBER 3 (WNT3), MRNA"
NM_001345	0.59	"HOMO SAPIENS DIACYLGLYCEROL KINASE, ALPHA (80KD) (DGKA), MRNA."
NM_014824	0.59	"HOMO SAPIENS KIAA0769 GENE PRODUCT (KIAA0769), MRNA."
AF288992	0.59	"HOMO SAPIENS 15 KDA SELENOPROTEIN (SEP15) GENE, COMPLETE CDS"
AK025134	0.59	"HOMO SAPIENS CDNA: FLJ21481 FIS, CLONE COL05066"
NM_001387	0.59	"HOMO SAPIENS DIHYDROPYRIMIDINASE-LIKE 3 (DPYSL3), MRNA."
AY074491	0.59	"HOMO SAPIENS EEG1S (EEG1) MRNA, COMPLETE CDS; ALTERNATIVELY SPLICED"
1138110.2	0.59	NULL
NM_018647	0.59	"HOMO SAPIENS TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY, MEMBER 19 (TNFRSF19), MRNA"
NM_012124	0.59	"HOMO SAPIENS CYSTEINE AND HISTIDINE-RICH DOMAIN (CHORD)-CONTAINING, ZINC BINDING PROTEIN 1 (CHORDC1), MRNA."
NM_005139	0.59	"HOMO SAPIENS ANNEXIN A3 (ANXA3), MRNA."
NM_004964	0.59	"HOMO SAPIENS HISTONE DEACETYLASE 1 (HDAC1), MRNA."
Y00815	0.59	HUMAN MRNA FOR LCA-HOMOLOG. LAR PROTEIN (LEUKOCYTE ANTIGEN RELATED)
NM_006336	0.59	"HOMO SAPIENS ZYG HOMOLOG (ZYG), MRNA."
X15804	0.59	HUMAN MRNA FOR ALPHA-ACTININ
AK021570	0.59	"HOMO SAPIENS CDNA FLJ11508 FIS, CLONE HEMBA1002162"
X69654	0.59	H.SAPIENS MRNA FOR RIBOSOMAL PROTEIN S26
NM_025085	0.59	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ13340 (FLJ13340), TRANSCRIPT VARIANT 2, MRNA"
AJ251973	0.59	HOMO SAPIENS PARTIAL STEERIN-1 GENE
NM_005936	0.59	"HOMO SAPIENS MYELOID/LYMPHOID OR MIXED-LINEAGE LEUKEMIA (TRITHORAX HOMOLOG, DROSOPHILA); TRANSLOCATED TO, 4 (MLLT4), MRNA"
NM_001216	0.59	"HOMO SAPIENS CARBONIC ANHYDRASE IX (CA9), MRNA."
NM_005560	0.60	"HOMO SAPIENS LAMININ, ALPHA 5 (LAMA5), MRNA"
NM_018227	0.60	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10808 (FLJ10808), MRNA."
NM_007355	0.60	"HOMO SAPIENS HEAT SHOCK 90KD PROTEIN 1, BETA (HSPCB), MRNA."
NM_003657	0.60	"HOMO SAPIENS BREAST CARCINOMA AMPLIFIED SEQUENCE 1 (BCAS1), MRNA."
NM_003107	0.60	"HOMO SAPIENS SRY (SEX DETERMINING REGION Y)-BOX 4 (SOX4), MRNA."
NM_020665	0.60	"HOMO SAPIENS KIDNEY-SPECIFIC MEMBRANE PROTEIN (NX-17), MRNA."
AB033025	0.60	"HOMO SAPIENS MRNA FOR KIAA1199 PROTEIN, PARTIAL CDS"
NM_014330	0.60	"HOMO SAPIENS PROTEIN PHOSPHATASE 1, REGULATORY (INHIBITOR) SUBUNIT 15A (PPP1R15A), MRNA"
NM_001946	0.60	"HOMO SAPIENS DUAL SPECIFICITY PHOSPHATASE 6 (DUSP6), TRANSCRIPT VARIANT 1, MRNA"
NM_031449	0.60	"HOMO SAPIENS KIAA1886 PROTEIN (DKFZP761I2123), MRNA."
AK023110	0.60	"HOMO SAPIENS CDNA FLJ13048 FIS, CLONE NT2RP3001399, WEAKLY SIMILAR TO SSU72 PROTEIN"
NM_018669	0.60	"HOMO SAPIENS WD REPEAT DOMAIN 4 (WDR4), TRANSCRIPT VARIANT 1, MRNA"
NM_032649	0.60	"HOMO SAPIENS GLUTAMATE CARBOXYPEPTIDASE-LIKE PROTEIN 2 (CPGL2), MRNA"
AL122071	0.60	HOMO SAPIENS MRNA; CDNA DKFZP434H1235 (FROM CLONE DKFZP434H1235); PARTIAL CDS
NM_004672	0.60	"HOMO SAPIENS MITOGEN-ACTIVATED PROTEIN KINASE KINASE KINASE 6 (MAP3K6), MRNA"
AF085987	0.60	HOMO SAPIENS FULL LENGTH INSERT CDNA CLONE YU05C01
NM_030970	0.60	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC3771 (MGC3771), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AL137721	0.60	HOMO SAPIENS MRNA; CDNA DKFZP761H221 (FROM CLONE DKFZP761H221)
NM_006282	0.60	"HOMO SAPIENS SERINE/THREONINE KINASE 4 (STK4), MRNA"
AK023905	0.60	"HOMO SAPIENS CDNA FLJ13843 FIS, CLONE THYRO1000796"
BC021898	0.60	"HOMO SAPIENS, CLONE MGC:17284 IMAGE:4340257, MRNA, COMPLETE CDS"
M92843	0.60	"H.SAPIENS ZINC FINGER TRANSCRIPTIONAL REGULATOR MRNA, COMPLETE CDS"
NM_002276	0.60	"HOMO SAPIENS KERATIN 19 (KRT19), MRNA"
NM_004363	0.60	"HOMO SAPIENS CARCINOEMBRYONIC ANTIGEN-RELATED CELL ADHESION MOLECULE 5 (CEACAM5), MRNA"
NM_002273	0.61	"HOMO SAPIENS KERATIN 8 (KRT8), MRNA"
BF663771	0.61	602145203F1 HOMO SAPIENS CDNA 5' END
M14333	0.61	"GNL|UG|HS#S341910 HOMO SAPIENS C-SYN PROTOONCOGENE MRNA, COMPLETE CDS /CDS=(579,2192) /GB=M14333 /GI=181171 /UG=HS.169370 /LEN=2647"
NM_033292	0.61	"HOMO SAPIENS CASPASE 1, APOPTOSIS-RELATED CYSTEINE PROTEASE (INTERLEUKIN 1, BETA, CONVERTASE) (CASP1), TRANSCRIPT VARIANT ALPHA, MRNA."
BC003641	0.61	"HOMO SAPIENS, CLONE MGC:4645 IMAGE:3529568, MRNA, COMPLETE CDS"
NM_030760	0.61	"HOMO SAPIENS ENDOTHELIAL DIFFERENTIATION, SPHINGOLIPID G-PROTEIN-COUPLED RECEPTOR, 8 (EDG8), MRNA"
BC003693	0.61	"HOMO SAPIENS, SIMILAR TO RIKEN CDNA 3930401K13 GENE, CLONE IMAGE:3454556, MRNA, PARTIAL CDS"
NM_000930	0.61	"HOMO SAPIENS PLASMINOGEN ACTIVATOR, TISSUE (PLAT), TRANSCRIPT VARIANT 1, MRNA"
NM_018096	0.61	"HOMO SAPIENS HYPOTHETICAL PROTEIN SIMILAR TO BETA-TRANSDUCIN FAMILY (FLJ10458), MRNA."
NM_001240	0.61	"HOMO SAPIENS CYCLIN T1 (CCNT1), MRNA."
NM_001299	0.61	"HOMO SAPIENS CALPONIN 1, BASIC, SMOOTH MUSCLE (CNN1), MRNA"
NM_001621	0.61	"HOMO SAPIENS ARYL HYDROCARBON RECEPTOR (AHR), MRNA."
NM_005082	0.61	"HOMO SAPIENS ZINC FINGER PROTEIN 147 (ESTROGEN-RESPONSIVE FINGER PROTEIN) (ZNF147), MRNA."
NM_004845	0.61	"HOMO SAPIENS PHOSPHATE CYTIDYLYLTRANSFERASE 1, CHOLINE, BETA ISOFORM (PCYT1B), MRNA."
NM_003286	0.61	"HOMO SAPIENS TOPOISOMERASE (DNA) I (TOP1), MRNA."
NM_144660	0.61	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ25082 (FLJ25082), MRNA"
NM_004904	0.61	"HOMO SAPIENS CAMP RESPONSE ELEMENT-BINDING PROTEIN CRE-BPA (H_GS165L15.1), MRNA"
AB033075	0.61	"HOMO SAPIENS MRNA FOR KIAA1249 PROTEIN, PARTIAL CDS"
NM_020239	0.61	"HOMO SAPIENS SMALL PROTEIN EFFECTOR 1 OF CDC42 (SPEC1), MRNA"
NM_005902	0.61	"HOMO SAPIENS MAD, MOTHERS AGAINST DECAPENTAPLEGIC HOMOLOG 3 (DROSOPHILA) (MADH3), MRNA"
NM_014296	0.61	"HOMO SAPIENS CALPAIN 7 (CAPN7), MRNA."
NM_025049	0.61	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ22692 (FLJ22692), MRNA"
NM_001674	0.61	"HOMO SAPIENS ACTIVATING TRANSCRIPTION FACTOR 3 (ATF3), MRNA"
NM_021960	0.61	"HOMO SAPIENS MYELOID CELL LEUKEMIA SEQUENCE 1 (BCL2-RELATED) (MCL1), MRNA"
NM_024498	0.61	"HOMO SAPIENS ZINC FINGER PROTEIN 117 (HPF9) (ZNF117), MRNA"
NM_018006	0.61	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10140 (FLJ10140), MRNA"
NM_001124	0.61	"HOMO SAPIENS ADRENOMEDULLIN (ADM), MRNA."
NM_016377	0.61	"HOMO SAPIENS A KINASE (PRKA) ANCHOR PROTEIN 7 (AKAP7), MRNA."
AK026965	0.61	"HOMO SAPIENS CDNA: FLJ23312 FIS, CLONE HEP11874"
NM_031944	0.61	"HOMO SAPIENS MIX-LIKE HOMEOBOX PROTEIN 1 (MILD1), MRNA"
AK023426	0.61	"HOMO SAPIENS CDNA FLJ13364 FIS, CLONE PLACE1000292"
NM_058189	0.61	"HOMO SAPIENS CHROMOSOME 21 OPEN READING FRAME 69 (C21ORF69), MRNA"
1502211.1	0.61	NULL
NM_023008	0.62	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12949 (FLJ12949), MRNA"
NM_004706	0.62	"HOMO SAPIENS RHO GUANINE NUCLEOTIDE EXCHANGE FACTOR (GEF) 1 (ARHGEF1), MRNA."
NM_001619	0.62	"HOMO SAPIENS ADRENERGIC, BETA, RECEPTOR KINASE 1 (ADRBK1), MRNA"
NM_003952	0.62	"HOMO SAPIENS RIBOSOMAL PROTEIN S6 KINASE, 70KD, POLYPEPTIDE 2 (RPS6KB2), MRNA."

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_003407	0.62	"HOMO SAPIENS ZINC FINGER PROTEIN 36, C3H TYPE, HOMOLOG (MOUSE) (ZFP36), MRNA."
1400651.5	0.62	NULL
NM_013275	0.62	"HOMO SAPIENS NASOPHARYNGEAL CARCINOMA SUSCEPTIBILITY PROTEIN (LZ16), MRNA."
X62006	0.62	H.SAPIENS PTB-1 GENE FOR POLYPIRIMIDINE TRACT BINDING PROTEIN
NM_001949	0.62	"HOMO SAPIENS E2F TRANSCRIPTION FACTOR 3 (E2F3) MRNA, COMPLETE CDS."
NM_145006	0.62	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC26847 (MGC26847), MRNA"
NM_145252	0.62	"HOMO SAPIENS SIMILAR TO COMMON SALIVARY PROTEIN 1 (LOC124220), MRNA"
NM_003414	0.62	"HOMO SAPIENS ZINC FINGER PROTEIN 267 (ZNF267), TRANSCRIPT VARIANT 498723, MRNA."
NM_017818	0.62	"HOMO SAPIENS WD REPEAT DOMAIN 8 (WDR8), MRNA."
NM_022343	0.62	"HOMO SAPIENS CHROMOSOME 9 OPEN READING FRAME 19 (C9ORF19), MRNA"
AL163305	0.62	NULL
NM_016014	0.62	"HOMO SAPIENS CGI-67 PROTEIN (LOC51104), MRNA."
NM_005969	0.62	"HOMO SAPIENS NUCLEOSOME ASSEMBLY PROTEIN 1-LIKE 4 (NAP1L4), MRNA."
NM_002939	0.62	"HOMO SAPIENS RIBONUCLEASE/ANGIOGENIN INHIBITOR (RNH), MRNA."
101314.1	0.62	NULL
NM_016123	0.62	"HOMO SAPIENS PUTATIVE PROTEIN KINASE NY-REN-64 ANTIGEN (LOC51135), MRNA."
NM_016265	0.62	"HOMO SAPIENS GIOT-3 FOR GONADOTROPIN INDUCIBLE TRANSCRIPTION REPRESSOR-3 (GIOT-3), MRNA."
NM_032873	0.62	"HOMO SAPIENS NM23-PHOSPHORYLATED UNKNOWN SUBSTRATE (MGC15437), MRNA"
NM_030575	0.62	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC10334 (MGC10334), MRNA."
NM_032678	0.62	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC3413 (MGC3413), MRNA"
AF025772	0.62	"HOMO SAPIENS C2H2 ZINC FINGER PROTEIN (ZNF189) GENE, ALTERNATIVE SPLICE PRODUCTS, COMPLETE CDS"
AK025461	0.62	"HOMO SAPIENS CDNA: FLJ21808 FIS, CLONE HEP00851, HIGHLY SIMILAR TO AF151843 HOMO SAPIENS CGI-85 PROTEIN MRNA"
NM_001461	0.62	"HOMO SAPIENS FLAVIN CONTAINING MONOOXYGENASE 5 (FMO5), MRNA."
AK027136	0.62	"HOMO SAPIENS CDNA: FLJ23483 FIS, CLONE KAIA04052"
NM_003683	0.62	"HOMO SAPIENS DNA SEGMENT ON CHROMOSOME 21 (UNIQUE) 2056 EXPRESSED SEQUENCE (D21S2056E), MRNA."
NM_004218	0.62	"HOMO SAPIENS RAB11B, MEMBER RAS ONCOGENE FAMILY (RAB11B), MRNA"
NM_004207	0.62	"HOMO SAPIENS SOLUTE CARRIER FAMILY 16 (MONOCARBOXYLIC ACID TRANSPORTERS), MEMBER 3 (SLC16A3), MRNA."
NM_006781	0.62	"HOMO SAPIENS CHROMOSOME 6 OPEN READING FRAME 10 (C6ORF10), MRNA."
AF075019	0.62	HOMO SAPIENS FULL LENGTH INSERT CDNA YI29A01
NM_012319	0.62	"HOMO SAPIENS LIV-1 PROTEIN, ESTROGEN REGULATED (LIV-1), MRNA."
NM_004447	0.62	"HOMO SAPIENS EPIDERMAL GROWTH FACTOR RECEPTOR PATHWAY SUBSTRATE 8 (EPS8), MRNA."
NM_024616	0.62	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ23186 (FLJ23186), MRNA"
NM_004766	0.62	"HOMO SAPIENS COATOMER PROTEIN COMPLEX, SUBUNIT BETA 2 (BETA PRIME) (COPB2), MRNA."
NM_005735	0.62	"HOMO SAPIENS ARP1 ACTIN-RELATED PROTEIN 1 HOMOLOG B, CENTRACTIN BETA (YEAST) (ACTR1B), MRNA."
BC007722	0.62	"HOMO SAPIENS, GLYCYL-TRNA SYNTHETASE, CLONE MGC:12625 IMAGE:4299853, MRNA, COMPLETE CDS"
NM_016076	0.62	"HOMO SAPIENS CGI-146 PROTEIN (LOC51029), MRNA."
NM_018226	0.62	"HOMO SAPIENS ARGINYL AMINOPEPTIDASE (AMINOPEPTIDASE B)-LIKE 1 (RNPEPL1), MRNA."
NM_015995	0.63	"HOMO SAPIENS KRUPPEL-LIKE FACTOR 13 (KLF13), MRNA."
NM_001647	0.63	"HOMO SAPIENS APOLIPOPROTEIN D (APOD), MRNA"
BQ720870	0.63	AGENCOURT_8296718 HOMO SAPIENS CDNA 5' END
NM_002850	0.63	"HOMO SAPIENS PROTEIN TYROSINE PHOSPHATASE, RECEPTOR TYPE, S (PTPRS), MRNA."
AK024447	0.63	"HOMO SAPIENS MRNA FOR FLJ00037 PROTEIN, PARTIAL CDS"
NM_019058	0.63	"HOMO SAPIENS HIF-1 RESPONSIVE RTP801 (RTP801), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
BC016029	0.63	"HOMO SAPIENS, CLONE MGC:16974 IMAGE:3921313, MRNA, COMPLETE CDS"
BI906953	0.63	"HUMAN ERK5 MRNA, COMPLETE CDS."
NM_030578	0.63	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC4093 (MGC4093), MRNA"
AB011539	0.63	"HOMO SAPIENS MRNA FOR MEGF6 PROTEIN (KIAA0815), PARTIAL CDS"
NM_003995	0.63	"HOMO SAPIENS NATRIURETIC PEPTIDE RECEPTOR B/GUANYLATE CYCLASE B (ATRIONATRIURETIC PEPTIDE RECEPTOR B) (NPR2), MRNA."
U24152	0.63	"P21 ACTIVATED KINASE 1, A SERINE-THREONINE KINASE THAT IS ACTIVATED BY THE RHO-RELATED GTPASES CDC42 AND RAC1, INVOLVED IN REGULATION OF MAP KINASE CASCADES, CYTOSKELETAL CHANGES ASSOCIATED WITH CELL POLARITY AND MIGRATION, AND INHIBITION OF APOPTOSIS"
331232.27	0.63	"ERYTHROCYTE MEMBRANE PROTEIN BAND 4.9 (DEMATIN), A MEMBER OF THE VILLIN SUPERFAMILY, BINDS AND BUNDLES ACTIN, MAY CONTROL CELL SHAPE AND SIZE, MAY BE INVOLVED IN PROSTATE TUMORIGENESIS"
1502800.17	0.63	"PROTEIN OF UNKNOWN FUNCTION, HAS LOW SIMILARITY TO UNCHARACTERIZED C. ELEGANS F08G12.1"
NM_019063	0.63	"HOMO SAPIENS CHROMOSOME 2 OPEN READING FRAME 2 (C2ORF2), MRNA."
NM_006391	0.63	"HOMO SAPIENS RAN BINDING PROTEIN 7 (RANBP7), MRNA"
NM_005572	0.63	"HOMO SAPIENS LAMIN A/C (LMNA), MRNA"
NM_004403	0.63	"HOMO SAPIENS DEAFNESS, AUTOSOMAL DOMINANT 5 (DFNA5), MRNA."
AK025703	0.63	"HOMO SAPIENS CDNA: FLJ22050 FIS, CLONE HEP09454"
BC022091	0.63	"HOMO SAPIENS, SIMILAR TO SIDEROFLEXIN 2, CLONE MGC:4567 IMAGE:3029622, MRNA, COMPLETE CDS"
NM_018294	0.63	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10998 (FLJ10998), MRNA."
NM_032179	0.63	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20542 (FLJ20542), MRNA."
NM_002670	0.63	"HOMO SAPIENS PLASTIN 1 (I ISOFORM) (PLS1), MRNA."
NM_025019	0.63	"HOMO SAPIENS LIKELY ORTHOLOG OF MOUSE TUBULIN ALPHA 4 (FLJ13940), MRNA"
NM_005962	0.63	"HOMO SAPIENS MAX INTERACTING PROTEIN 1 (MXI1), MRNA."
AF079099	0.63	"HOMO SAPIENS ARGININE-TRNA-PROTEIN TRANSFERASE 1-2P (ATE1) MRNA, ALTERNATIVELY SPLICED PRODUCT, PARTIAL CDS"
NM_152905	0.63	"HOMO SAPIENS NEURAL PRECURSOR CELL EXPRESSED, DEVELOPMENTALLY DOWN-REGULATED 1 (NEDD1), MRNA"
NM_012329	0.63	"HOMO SAPIENS MONOCYTE TO MACROPHAGE DIFFERENTIATION-ASSOCIATED (MMD), MRNA."
NM_016428	0.63	"HOMO SAPIENS NESH PROTEIN (NESH), MRNA."
NM_033490	0.63	"HOMO SAPIENS CELL DIVISION CYCLE 2-LIKE 1 (PITSLRE PROTEINS) (CDC2L1), TRANSCRIPT VARIANT 6, MRNA"
AK021583	0.63	"HOMO SAPIENS CDNA FLJ11521 FIS, CLONE HEMBA1002486"
NM_031991	0.63	"HOMO SAPIENS POLYPYRIMIDINE TRACT BINDING PROTEIN (HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN I) (PTB), TRANSCRIPT VARIANT 3, MRNA."
AL137663	0.63	HOMO SAPIENS MRNA; CDNA DKFZP434G227 (FROM CLONE DKFZP434G227)
AK056644	0.63	"HOMO SAPIENS CDNA FLJ32082 FIS, CLONE OCBBF2000231, WEAKLY SIMILAR TO PHOSPHOLIPASE A2 INHIBITOR SUBUNIT B PRECURSOR"
NM_032587	0.63	"HOMO SAPIENS CASPASE RECRUITMENT DOMAIN FAMILY, MEMBER 6 (CARD6), MRNA"
NM_002115	0.63	"HOMO SAPIENS HEXOKINASE 3 (WHITE CELL) (HK3), NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, MRNA."
NM_024677	0.64	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ14001 (FLJ14001), MRNA"
NM_016262	0.64	"HOMO SAPIENS EPSILON-TUBULIN (LOC51175), MRNA."
NM_024595	0.64	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ12666 (FLJ12666), MRNA"
AB023211	0.64	"HOMO SAPIENS MRNA FOR KIAA0994 PROTEIN, PARTIAL CDS"
NM_001902	0.64	"HOMO SAPIENS CYSTATHIONASE (CYSTATHIONINE GAMMA-LYASE) (CTH), MRNA."
NM_004593	0.64	"HOMO SAPIENS SPLICING FACTOR, ARGININE/SERINE-RICH 10 (TRANSFORMER 2 HOMOLOG, DROSOPHILA) (SFRS10), MRNA."
NM_007114	0.64	"HOMO SAPIENS TATA ELEMENT MODULATORY FACTOR 1 (TMF1), MRNA."
AK057059	0.64	"HOMO SAPIENS CDNA FLJ32497 FIS, CLONE SKNSH2000250, HIGHLY SIMILAR TO R.NORVEGICUS MRNA FOR K+ CHANNEL PROTEIN, BETA SUBUNIT"
NM_016120	0.64	"HOMO SAPIENS PUTATIVE RING ZINC FINGER PROTEIN NY-REN-43 ANTIGEN (LOC51132), MRNA."

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AL122046	0.64	HOMO SAPIENS MRNA; CDNA DKFZP434O0515 (FROM CLONE DKFZP434O0515)
BQ430788	0.64	AGENCOURT_7776027 HOMO SAPIENS CDNA 5' END
NM_000641	0.64	"HOMO SAPIENS INTERLEUKIN 11 (IL11), MRNA"
NM_145241	0.64	"HOMO SAPIENS SIMILAR TO SPERMATID WD-REPEAT PROTEIN (LOC114987), MRNA"
NM_000287	0.64	"HOMO SAPIENS PEROXISOMAL BIOGENESIS FACTOR 6 (PEX6), MRNA."
L47234 X65178	0.64 0.64	"HOMO SAPIENS ERCC2 (ERCC2) AND KINESIN LIGHT CHAIN (KLC2) GENES, COMPLETE CDS, COMPLETE SEQUENCE" H.SAPIENS GENE FOR SUBSTANCE P RECEPTOR (EXON 2)
BC012155	0.64	"HOMO SAPIENS, CLONE IMAGE:4561787, MRNA"
AE006466	0.64	HOMO SAPIENS 16P13.3 SEQUENCE SECTION 5 OF 8
NM_024096	0.64	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC5627 (MGC5627), MRNA"
NM_012484	0.64	"HOMO SAPIENS HYALURONAN-MEDIATED MOTILITY RECEPTOR (RHAMM) (HMMR), TRANSCRIPT VARIANT 1, MRNA"
AK026064	0.64	"HOMO SAPIENS CDNA: FLJ22411 FIS, CLONE HRC08456"
NM_003713	0.64	"HOMO SAPIENS PHOSPHATIDIC ACID PHOSPHATASE TYPE 2B (PPAP2B), MRNA."
NM_015437	0.64	"HOMO SAPIENS DKFZP586N0819 PROTEIN (DKFZP586N0819), MRNA"
AW328201	0.64	"DR04H10.X1 NIH_MGC_3 HOMO SAPIENS CDNA CLONE IMAGE:2847235 5', MRNA SEQUENCE"
NM_006247	0.64	"HOMO SAPIENS PROTEIN PHOSPHATASE 5, CATALYTIC SUBUNIT (PPP5C), MRNA."
AF051160	0.64	"HOMO SAPIENS TYROSINE PHOSPHATASE (PRL-1) GENE, COMPLETE CDS"
NM_002184	0.64	"HOMO SAPIENS INTERLEUKIN 6 SIGNAL TRANSDUCER (GP130, ONCOSTATIN M RECEPTOR) (IL6ST), MRNA."
AF047690	0.64	"HUMAN ATP-BINDING CASSETTE PROTEIN M-ABC1 MRNA, NUCLEAR GENE ENCODING MITOCHONDRIAL PROTEIN, COMPLETE CDS."
BG564693	0.64	"602589902F1 HOMO SAPIENS CDNA, 5' END"
NM_005239	0.64	"HOMO SAPIENS V-ETS ERYTHROBLASTOSIS VIRUS E26 ONCOGENE HOMOLOG 2 (AVIAN) (ETS2), MRNA"
NM_021131	0.64	"HOMO SAPIENS PROTEIN PHOSPHATASE 2A, REGULATORY SUBUNIT B' (PR 53) (PPP2R4), MRNA."
NM_003243	0.64	"HOMO SAPIENS TRANSFORMING GROWTH FACTOR, BETA RECEPTOR III (BETAGLYCAN, 300KD) (TGFBR3), MRNA."
BG535739	0.64	602563859F1 HOMO SAPIENS CDNA 5' END
NM_001087	0.64	"HOMO SAPIENS ANGIO-ASSOCIATED, MIGRATORY CELL PROTEIN (AAMP), MRNA."
NM_019011	0.64	"HOMO SAPIENS TRIAD3 PROTEIN (TRIAD3), MRNA."
NM_005660	0.64	"HOMO SAPIENS SOLUTE CARRIER FAMILY 35 (UDP-GALACTOSE TRANSPORTER), MEMBER 2 (SLC35A2), MRNA"
AK024739	0.64	"HOMO SAPIENS CDNA: FLJ21086 FIS, CLONE CAS03272"
AK055853	0.64	"HOMO SAPIENS CDNA FLJ31291 FIS, CLONE KIDNE2007356"
AB010443	0.64	"HOMO SAPIENS DNA, DLEC1 TO ORCTL4 GENE REGION, SECTION 1/2 (DLEC1, ORCTL3, ORCTL4 GENES, COMPLETE CDS)."
NM_002695	0.64	"HOMO SAPIENS POLYMERASE (RNA) II (DNA DIRECTED) POLYPEPTIDE E (25KD) (POLR2E), MRNA."
NM_018304	0.64	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ11029 (FLJ11029), MRNA"
NM_032484	0.64	"HOMO SAPIENS D11LGP1E-LIKE (LGP1), MRNA"
AL832781	0.64	HOMO SAPIENS MRNA; CDNA DKFZP686L057 (FROM CLONE DKFZP686L057)
NM_021027 NM_021993	0.64 0.64	"HOMO SAPIENS UDP GLYCOSYLTRANSFERASE 1 FAMILY, POLYPEPTIDE A9 (UGT1A9), MRNA." "HOMO SAPIENS FUS INTERACTING PROTEIN (SERINE-ARGININE RICH) 2 (FUSIP2), MRNA."
NM_014420	0.64	"HOMO SAPIENS DICKKOPF HOMOLOG 4 (XENOPUS LAEVIS) (DKK4), MRNA"
BC015931	0.64	"HOMO SAPIENS, RAB35, MEMBER RAS ONCOGENE FAMILY, CLONE MGC:8924 IMAGE:3907209, MRNA, COMPLETE CDS"
NM_006706	0.64	"HOMO SAPIENS TRANSCRIPTION ELONGATION REGULATOR 1 (CA150) (TCERG1), MRNA"
AF155117	0.64	"HOMO SAPIENS NY-REN-62 ANTIGEN MRNA, PARTIAL CDS"
AB033086	0.65	"HOMO SAPIENS MRNA FOR KIAA1260 PROTEIN, PARTIAL CDS"
NM_000666	0.65	"HOMO SAPIENS AMINOACYLASE 1 (ACY1), MRNA."
NM_052932	0.65	"HOMO SAPIENS PRO-ONCOSIS RECEPTOR INDUCING MEMBRANE INJURY GENE (PORIMIN), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
NM_005605	0.65	"HOMO SAPIENS PROTEIN PHOSPHATASE 3 (FORMERLY 2B), CATALYTIC SUBUNIT, GAMMA ISOFORM (CALCINEURIN A GAMMA) (PPP3CC), MRNA."
BC036771	0.65	"HOMO SAPIENS, CLONE MGC:46680 IMAGE:5576828, MRNA, COMPLETE CDS"
NM_000433	0.65	"HOMO SAPIENS NEUTROPHIL CYTOSOLIC FACTOR 2 (65KD, CHRONIC GRANULOMATOUS DISEASE, AUTOSOMAL 2) (NCF2), MRNA."
NM_007198	0.65	"HOMO SAPIENS PROLINE SYNTHETASE CO-TRANSCRIBED HOMOLOG (BACTERIAL) (PROSC), MRNA"
AB028645	0.65	"HOMO SAPIENS MRNA FOR CBL-C, COMPLETE CDS"
NM_004040	0.65	"HOMO SAPIENS RAS HOMOLOG GENE FAMILY, MEMBER B (ARHB), MRNA"
AK096820	0.65	"HOMO SAPIENS CDNA FLJ39501 FIS, CLONE PROST2016980, MODERATELY SIMILAR TO CYTOCHROME P450 4F2 (EC 1.14.13.30)"
NM_007054	0.65	"HOMO SAPIENS KINESIN FAMILY MEMBER 3A (KIF3A), MRNA."
NM_002227	0.65	"HOMO SAPIENS JANUS KINASE 1 (A PROTEIN TYROSINE KINASE) (JAK1), MRNA."
NM_030674	0.65	"HOMO SAPIENS AMINO ACID TRANSPORTER SYSTEM A1 (ATA1), MRNA."
AB025432	0.65	"HOMO SAPIENS MRNA FOR GILZ, COMPLETE CDS"
NM_015945	0.65	"HOMO SAPIENS OVARIAN CANCER OVEREXPRESSED 1 (OVCOV1), MRNA"
BC012362	0.65	"HOMO SAPIENS, CLONE MGC:20484 IMAGE:4650072, MRNA, COMPLETE CDS"
NM_020993	0.65	"HOMO SAPIENS B-CELL CLL/LYMPHOMA 7A (BCL7A), MRNA"
NM_032219	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ22269 (FLJ22269), MRNA."
NM_024604	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ21908 (FLJ21908), MRNA"
NM_004203	0.65	"HOMO SAPIENS MEMBRANE-ASSOCIATED TYROSINE- AND THREONINE-SPECIFIC CDC2-INHIBITORY KINASE (PKMYT1), MRNA"
NM_005979	0.65	"HOMO SAPIENS S100 CALCIUM BINDING PROTEIN A13 (S100A13), MRNA."
1075733.1	0.65	NULL
BG678787	0.65	602624339F1 HOMO SAPIENS CDNA 5' END
AK021872	0.65	"HOMO SAPIENS CDNA FLJ11810 FIS, CLONE HEMBA1006347, MODERATELY SIMILAR TO MALES-ABSENT ON THE FIRST PROTEIN (EC 2.3.1.-)"
NM_022114	0.65	"HOMO SAPIENS PR DOMAIN CONTAINING 16 (PRDM16), MRNA"
NM_002834	0.65	"HOMO SAPIENS PROTEIN TYROSINE PHOSPHATASE, NON-RECEPTOR TYPE 11 (PTPN11), TRANSCRIPT VARIANT 1, MRNA"
NM_003468	0.65	"HOMO SAPIENS FRIZZLED HOMOLOG 5 (DROSOPHILA) (FZD5), MRNA"
NM_016022	0.65	"HOMO SAPIENS CGI-78 PROTEIN (LOC51107), MRNA."
BC001096	0.65	"HOMO SAPIENS, CLONE IMAGE:3507281, MRNA, PARTIAL CDS"
NM_032769	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC16212 (MGC16212), MRNA"
AF118108	0.65	"HOMO SAPIENS LYMPHATIC ENDOTHELIUM-SPECIFIC HYALURONAN RECEPTOR LYVE-1 MRNA, COMPLETE CDS"
NM_005276	0.65	"HOMO SAPIENS GLYCEROL-3-PHOSPHATE DEHYDROGENASE 1 (SOLUBLE) (GPD1), MRNA"
NM_015621	0.65	"HOMO SAPIENS DKFZP434C171 PROTEIN (DKFZP434C171), MRNA."
NM_004749	0.65	"HOMO SAPIENS CELL CYCLE PROGRESSION 2 PROTEIN (CPR2), MRNA."
AF088062	0.65	HOMO SAPIENS FULL LENGTH INSERT CDNA CLONE ZD74E10
1082602.1	0.65	"PROTEIN WITH HIGH SIMILARITY TO ZINC-FINGER PROTEIN (HUMAN ZNF10), WHICH INHIBITS SOME COMPONENTS OF RNA POLYMERASE II AND III TRANSCRIPTION, CONTAINS FIFTEEN C2H2 TYPE ZINC FINGER DOMAINS, WHICH BIND NUCLEIC ACIDS"
AF037448	0.65	"HOMO SAPIENS RRM RNA BINDING PROTEIN GRY-RBP (GRY-RBP) MRNA, COMPLETE CDS"
NM_030792	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN PP1665 (PP1665), MRNA"
AF113511	0.65	"HOMO SAPIENS INTEGRIN SUBUNIT ALPHA-2 (ITGA2) GENE, ITGA2-2 ALLELE, 3'UTR"
NM_005433	0.65	"HOMO SAPIENS V-YES-1 YAMAGUCHI SARCOMA VIRAL ONCOGENE HOMOLOG 1 (YES1), MRNA."
NM_020123	0.65	"HOMO SAPIENS ENDOMEMBRANE PROTEIN EMP70 PRECURSOR ISOLOG (LOC56889), MRNA."
AP000500	0.65	"HOMO SAPIENS GENOMIC DNA, CHROMOSOME 3P21.3, CLONE:603 TO 320, ANTI-ONCOGENE REGION, SECTION 3/3"
BC012170	0.65	"HOMO SAPIENS, SIMILAR TO RIKEN CDNA 6230427J02 GENE, CLONE MGC:20416 IMAGE:4642270, MRNA, COMPLETE CDS"
D50683	0.65	"HOMO SAPIENS MRNA FOR TGF-BETAIIR ALPHA, COMPLETE CDS"
NM_003236	0.65	"HOMO SAPIENS TRANSFORMING GROWTH FACTOR, ALPHA (TGFA), MRNA."

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
AB058760	0.65	"HOMO SAPIENS MRNA FOR KIAA1857 PROTEIN, PARTIAL CDS"
BM724842	0.65	"UI-E-EJ0-AIS-H-20-0-UI.R1 HOMO SAPIENS CDNA, 5' END"
NM_003244	0.65	"HOMO SAPIENS TGFB-INDUCED FACTOR (TALE FAMILY HOMEOBOX) (TGIF), MRNA."
NM_018986	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN (FLJ20356), MRNA."
NM_016629	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN (LOC51323), MRNA."
NM_005787	0.65	"HOMO SAPIENS NOT56 (D. MELANOGASTER)-LIKE PROTEIN (NOT56L), MRNA."
NM_004357	0.65	"HOMO SAPIENS CD151 ANTIGEN (CD151), TRANSCRIPT VARIANT 1, MRNA"
NM_144643	0.65	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ30655 (FLJ30655), MRNA"
BC018130	0.65	"HOMO SAPIENS, COAGULATION FACTOR II (THROMBIN) RECEPTOR-LIKE 1, CLONE MGC:9298 IMAGE:3895653, MRNA, COMPLETE CDS"
NM_000426	0.65	"HOMO SAPIENS LAMININ, ALPHA 2 (MEROSIN, CONGENITAL MUSCULAR DYSTROPHY) (LAMA2), MRNA."
AK024835	0.65	"HOMO SAPIENS CDNA: FLJ21182 FIS, CLONE CAS11560, HIGHLY SIMILAR TO D83735 HOMO SAPIENS MRNA FOR NEUTRAL CALPONIN"
NM_007034	0.65	"HOMO SAPIENS DNAJ (HSP40) HOMOLOG, SUBFAMILY B, MEMBER 4 (DNAJB4), MRNA."
BQ430527	0.66	AGENCOURT_7723632 HOMO SAPIENS CDNA 5' END
NM_015533	0.66	"HOMO SAPIENS DKFZP586B1621 PROTEIN (DKFZP586B1621), MRNA"
NM_006386	0.66	"HOMO SAPIENS DEAD/H (ASP-GLU-ALA-ASP/HIS) BOX POLYPEPTIDE 17 (72KD) (DDX17), TRANSCRIPT VARIANT 1, MRNA."
NM_004417	0.66	"HOMO SAPIENS DUAL SPECIFICITY PHOSPHATASE 1 (DUSP1), MRNA."
NM_002350	0.66	"HOMO SAPIENS V-YES-1 YAMAGUCHI SARCOMA VIRAL RELATED ONCOGENE HOMOLOG (LYN), MRNA."
AK024950	0.66	"HOMO SAPIENS CDNA: FLJ21297 FIS, CLONE COL02035"
NM_001283	0.66	"HOMO SAPIENS ADAPTOR-RELATED PROTEIN COMPLEX 1, SIGMA 1 SUBUNIT (AP1S1), TRANSCRIPT VARIANT 1, MRNA."
NM_004387	0.66	"HOMO SAPIENS CARDIAC-SPECIFIC HOMEO BOX (CSX), MRNA."
NM_013311	0.66	"HOMO SAPIENS INSULIN PROMOTER FACTOR 1, HOMEODOMAIN TRANSCRIPTION FACTOR (IPF1), MRNA"
NM_014604	0.66	"HOMO SAPIENS TAX INTERACTION PROTEIN 1 (TIP-1), MRNA"
AJ229040	0.66	HOMO SAPIENS 959 KB CONTIG BETWEEN AML1 AND CBR1 ON CHROMOSOME 21Q22
AL117595	0.66	HOMO SAPIENS MRNA; CDNA DKFZP564C2063 (FROM CLONE DKFZP564C2063)
NM_005384	0.66	"HOMO SAPIENS NUCLEAR FACTOR, INTERLEUKIN 3 REGULATED (NFIL3), MRNA."
AK024490	0.66	"HOMO SAPIENS MRNA FOR FLJ00092 PROTEIN, PARTIAL CDS"
NM_016084	0.66	"HOMO SAPIENS RAS, DEXAMETHASONE-INDUCED 1 (RASD1), MRNA."
NM_004999	0.66	"HOMO SAPIENS MYOSIN VI (MYO6), MRNA."
NM_006844	0.66	"HOMO SAPIENS ILVB (BACTERIAL ACETOLACTATE SYNTHASE)-LIKE (ILVBL), MRNA."
NM_018015	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10178 (FLJ10178), MRNA"
NM_032287	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP761O17121 (DKFZP761O17121), MRNA."
U32642	0.66	"HUMAN H4 GENE, INTRON 1, PARTIAL SEQUENCE"
NM_080385	0.66	"HOMO SAPIENS CARBOXYPEPTIDASE A5 (CPA5), MRNA"
AF132811	0.66	"HOMO SAPIENS NECTIN-LIKE PROTEIN 2 (NECL2) MRNA, COMPLETE CDS"
U09847	0.66	"HUMAN ZINC FINGER PROTEIN (ZNF138) MRNA, PARTIAL CDS"
NM_014770	0.66	"HOMO SAPIENS CENTAURIN, GAMMA 1 (CENTG1), MRNA"
NM_016016	0.66	"HOMO SAPIENS CGI-69 PROTEIN (LOC51629), MRNA"
NM_004099	0.66	"HOMO SAPIENS ERYTHROCYTE MEMBRANE PROTEIN BAND 7.2 (STOMATIN) (EPB72), MRNA"
NM_018347	0.66	"HOMO SAPIENS CHROMOSOME 20 OPEN READING FRAME 29 (C20ORF29), MRNA."
NM_002895	0.66	"HOMO SAPIENS RETINOBLASTOMA-LIKE 1 (P107) (RBL1), MRNA"
AB033093	0.66	"HOMO SAPIENS MRNA FOR KIAA1267 PROTEIN, PARTIAL CDS"
BC000712	0.66	"HOMO SAPIENS, SIMILAR TO KINESIN FAMILY MEMBER C1, CLONE MGC:1202 IMAGE:3506669, MRNA, COMPLETE CDS"
NM_003897	0.66	"HOMO SAPIENS IMMEDIATE EARLY RESPONSE 3 (IER3), TRANSCRIPT VARIANT SHORT, MRNA."
NM_018725	0.66	"HOMO SAPIENS INTERLEUKIN 17B RECEPTOR (IL17BR), MRNA"
NM_032307	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC10999 (MGC10999), MRNA"
NM_025008	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ13544 (FLJ13544), MRNA"

Appendix 3

Accession Number	Fold Change (Fex/DMSO)	Gene Description
Y14321	0.66	"HOMO SAPIENS PMP69 GENE, EXONS 8,9,10 & 11"
NM_024048	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC3020 (MGC3020), MRNA"
NM_025106	0.66	"HOMO SAPIENS SPRY DOMAIN-CONTAINING SOCS BOX PROTEIN SSB-1 (FLJ22393), MRNA."
NM_002906	0.66	"HOMO SAPIENS RADIXIN (RDX), MRNA"
NM_152338	0.66	"HOMO SAPIENS ZYMOGEN GRANULE PROTEIN 16 (ZG16), MRNA"
BC019623	0.66	"HOMO SAPIENS, CLONE IMAGE:4539469, MRNA, PARTIAL CDS"
AF218848	0.66	"HOMO SAPIENS BETA II SPECTRIN-SHORT ISOFORM MRNA, PARTIAL CDS"
NM_006313	0.66	"HOMO SAPIENS UBIQUITIN SPECIFIC PROTEASE 15 (USP15), MRNA."
M92300	0.66	"HUMAN HUMAN VOLTAGE-DEPENDENT CALCIUM CHANNEL BETA-1 SUBUNIT, EXONS 1-4"
AL163263	0.66	NULL
NM_030974	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN DKFZP434N1923 (DKFZP434N1923), MRNA"
NM_022139	0.66	"HOMO SAPIENS GDNF FAMILY RECEPTOR ALPHA 4 (GFRA4), TRANSCRIPT VARIANT 1, MRNA"
L44140	0.66	"HOMO SAPIENS CHROMOSOME X REGION FROM FILAMIN (FLN) GENE TO GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) GENE, COMPLETE CDS'S"
M87507	0.66	"HOMO SAPIEN INTERLEUKIN-1 BETA CONVERTASE (IL1BCE) MRNA, COMPLETE CDS"
NM_004095	0.66	"HOMO SAPIENS EUKARYOTIC TRANSLATION INITIATION FACTOR 4E BINDING PROTEIN 1 (EIF4EBP1), MRNA"
NM_080678	0.66	"HOMO SAPIENS NEDD8-CONJUGATING ENZYME (NCE2), MRNA"
NM_007097	0.66	"HOMO SAPIENS CLATHRIN, LIGHT POLYPEPTIDE (LCB) (CLTB), MRNA."
NM_020142	0.66	"HOMO SAPIENS NADH:UBIQUINONE OXIDOREDUCTASE MLRQ SUBUNIT HOMOLOG (LOC56901), MRNA"
NM_012141	0.66	"HOMO SAPIENS DEAD/H (ASP-GLU-ALA-ASP/HIS) BOX POLYPEPTIDE 26 (DDX26), MRNA."
NM_005257	0.66	"HOMO SAPIENS GATA BINDING PROTEIN 6 (GATA6), MRNA."
BC002766	0.66	"HOMO SAPIENS, SIMILAR TO KIAA0998 PROTEIN, CLONE MGC:4173 IMAGE:3632160, MRNA, COMPLETE CDS"
NM_002084	0.66	"HOMO SAPIENS GLUTATHIONE PEROXIDASE 3 (PLASMA) (GPX3), MRNA"
NM_017855	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ20513 (FLJ20513), MRNA"
AB018353	0.66	"HOMO SAPIENS MRNA FOR KIAA0810 PROTEIN, PARTIAL CDS"
NM_018475	0.66	"HOMO SAPIENS TPA REGULATED LOCUS (TPARL), MRNA"
NM_018078	0.66	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ10378 (FLJ10378), MRNA"
NM_017838	0.66	"HOMO SAPIENS NUCLEOLAR PROTEIN FAMILY A, MEMBER 2 (H/ACA SMALL NUCLEOLAR RNPS) (NOLA2), MRNA."
NM_005475	0.66	"HOMO SAPIENS LYMPHOCYTE ADAPTOR PROTEIN (LNK), MRNA."
NM_002961	0.66	"HOMO SAPIENS S100 CALCIUM BINDING PROTEIN A4 (CALCIUM PROTEIN, CALVASCULIN, METASTASIN, MURINE PLACENTAL HOMOLOG) (S100A4), TRANSCRIPT VARIANT 1, MRNA"
AL133626	0.67	HOMO SAPIENS MRNA; CDNA DKFZP434K0522 (FROM CLONE DKFZP434K0522)
X65644	0.67	H.SAPIENS MRNA MBP-2 FOR MHC BINDING PROTEIN 2
NM_006270	0.67	"HOMO SAPIENS RELATED RAS VIRAL (R-RAS) ONCOGENE HOMOLOG (RRAS), MRNA."
AK001674	0.67	"HOMO SAPIENS CDNA FLJ10812 FIS, CLONE NT2RP4000975"
NM_001980	0.67	"HOMO SAPIENS EPIMORPHIN (EPIM), MRNA."
AF125158	0.67	"HUMAN ZINC FINGER DNA BINDING PROTEIN 99 (ZNF281) MRNA, COMPLETE CDS."
NM_032310	0.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC11115 (MGC11115), MRNA"
NM_020423	0.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN LOC57147 (LOC57147), MRNA"
NM_001694	0.67	"HOMO SAPIENS ATPASE, H+ TRANSPORTING, LYSOSOMAL (VACUOLAR PROTON PUMP) 16KD (ATP6L), MRNA."
NM_014547	0.67	"HOMO SAPIENS TROPOMODULIN 3 (UBIQUITOUS) (TMOD3), MRNA"
NM_024874	0.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN FLJ14225 (FLJ14225), MRNA"
AF244812	0.67	"HOMO SAPIENS SCAN DOMAIN-CONTAINING PROTEIN 2 (SCAND2) GENE, COMPLETE CDS, ALTERNATIVELY SPLICED"
NM_024070	0.67	"HOMO SAPIENS HYPOTHETICAL PROTEIN MGC2463 (MGC2463), MRNA"